DESIGN AND EVALUATION OF CONTROLLED ONSET EXTENDED RELEASE (COER) PRESS-COATED TABLETS FOR CHRONOTHERAPEUTIC DELIVERY OF PROPRANOLOL HYDROCHLORIDE

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Certificate

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ABBREVIATIONS

API	-	Active pharmaceutical ingredient
BP	-	Blood pressure
COER	-	Controlled onset extended release
CR	-	Controlled release
CRDDS	-	Controlled release drug delivery systems
DBP	-	Diastolic blood pressure
EC	-	Ethyl cellulose
FTIR	-	Fourier transform infrared spectrometer
HPMC	-	Hydroxy propyl methyl cellulose
Hrs	-	Hours
ICH	-	International Conference on Harmonization
IP	-	Indian pharmacopoeia
JP	-	Japanese pharmacopoeia
MCC	-	Microcrystalline cellulose
MEC	-	Minimum effective concentration
Min	-	Minutes
Ph Eur	-	European pharmacopoeia
PCT	-	Press coated tablets
q.s	-	Quantum sufficit
SBP	-	Systolic blood pressure
TCDDS	-	Time controlled drug delivery system
USP	-	United States pharmacopoeia
UV	-	Ultra Violet

1. PURPOSE AND PLAN OF WORK

1.1 PURPOSE OF WORK

The purpose of the study is to develop Press coated tablets (PCT) of Propranolol Hcl for Chronotherapeutic delivery. Propranolol Hcl is used in the treatment of hypertension, arrhythmia, angina pectoris. According to circadian rhythm (24hr- Biological clock) the Blood pressure (BP) will be more in early morning 3a.m – 6a.m because renin, cortisol, angiotensin, aldosterone secretion is in peak level, most of the cardio vascular disorders such as Angina pectoris, sudden cardiac death, stroke, occurs in this time, the designed formulation to be taken at bed time and the focus is to optimally deliver the drug in higher amounts in early morning hours (i.e. at time of greatest need) and lower amounts at night (i.e. when the need of drug is less).

Propranolol is a highly lipophilic drug and is almost completely absorbed after oral administration. However, its bioavailability is very limited (30%) due to the hepatic first-pass effect. Its elimination half-life is also relatively short (about 2–6 h). Therefore, it was chosen as a model drug for preparation of the once-daily controlled onset extended release (COER) dosage form.

- An oral time controlled release formulation facilitates the administration, just once a day to control the BP in patient with morning surge, which results in better compliance by patients and fewer side effects.
- The main aim of the work is to achieve time-controlled release with distinct predetermined lag time.
- To study the effect of formulation of outer shell comprising both hydrophobic polymer and hydrophilic swellable polymers on the time lag of drug release.
- To find out the suitable weight ratios of polymers, to modulate the lag time.

- To study the drug release kinetics from data obtained through *in vitro* dissolution studies.

1.2 PLAN OF WORK

The present work was carried out in the following phases.

Phase 1 : Literature survey on chronotherapeutic delivery of propranolol Hcl drug and time controlled release dosage forms.

Phase 2 : Preformulation studies

Phase 3 : Formulation of time-controlled release press-coated tablets of propranolol Hcl using hydrophilic swellable excipients and hydrophobic polymers.

Phase 4 : Evaluation studies

Phase 5 : Drug release kinetics.

2. INTRODUCTION

2.1 Chronotherapeutic drug delivery system[1]

Chronotherapeutics is the delivery of medications in the right concentration to the right targeted tissues at the right time to meet biological rhythm-determined needs, e.g., rhythms in the mechanisms of disease, symptom intensity, and/or patient tolerance, to optimize therapeutic outcomes and minimize adverse effects.

"Chronopharmaceutics" consists of two words chronobiology and pharmaceutics. Chronobiology is the study of biological rhythms and their mechanisms.

A biologic rhythm is a self-sustaining oscillation. It is defined by its period, amplitude, and phasing. There are three types of biological rhythms in our body, they are:

i. Circadian rhythm
ii. Ultradian rhythm
iii. Infradian rhythm

Circadian rhythm: This word comes from latin word

"circa" means *about*

"dies" means *day*.

A rhythm with a period close or equal to 24 h is termed as circadian.

Ultradian rhythm:

Oscillation of shorter duration are termed as ultradian (more than one cycle per 24 h). Eg: High-frequency oscillations in electrical impulses of the brain and heart, and the pulsatile secretion of hormones.

Infradian rhythm:

Oscillations that are longer than 24 h (less than one cycle per day)

Example: Menstrual and seasonal oscillations

Table 1 : Spectrum of biologic rhythms[1]

Category of rhythms	Period of rhythms	Term used to describe rhythm	Illustrative examples
Short periods	≤ Sec	High frequency Oscillations	Electroencephalogram Electrocardiogram
Medium periods	30 min to 20 h 20 h to 28 h	Ultradian Circadian	Sleep staging Pulsatile hormone secretion Most biologic functions
Long periods	28 h to 6 days ~week ~Month ~Year	Infradian Circaseptan Circamensual Circannual	Little studied thus far Work–rest routine Menstruation, fertility Neuroendocrine functions. Many biochemical, endocrine, and Physiological parameters.

2.2 The circadian time structure[2]

The results of numerous biologic rhythm studies help to define the temporal organization of human beings. One means of illustrating the human circadian time structure is to depict the peak time of 24-h rhythms on a clock-like diagram shown in Fig. 1

- The peak in basal gastric acid secretion, white blood cell count (WBC), and calcitonin gene–related protein and atrial natriuretic peptides (both exerting BP–lowering effects) is late at night or early in sleep.
- Growth and thyroid stimulating hormone (TSH), blood lymphocyte and eosinophil number, and plasma concentration of melatonin and prolactin crest later in sleep,
- As do adrenocorticotropic hormone (ACTH), follicle stimulating hormone (FSH), and luteinizing (LH) hormone. Plasma cortisol, renin activity,angiotensin, and aldosterone crest in the morning as do arterial compliance, vascular resistance, platelet aggregation,

and blood viscosity.

- Hemoglobin and insulin are greatest in the afternoon. Serum cholesterol and triglycerides and urinary diuresis are highest early in the evening.

The information conveyed in this and other such figures clearly shows the biochemistry and physiology of human beings are not constant; rather, they are variable in a predictable manner during the 24-h period.

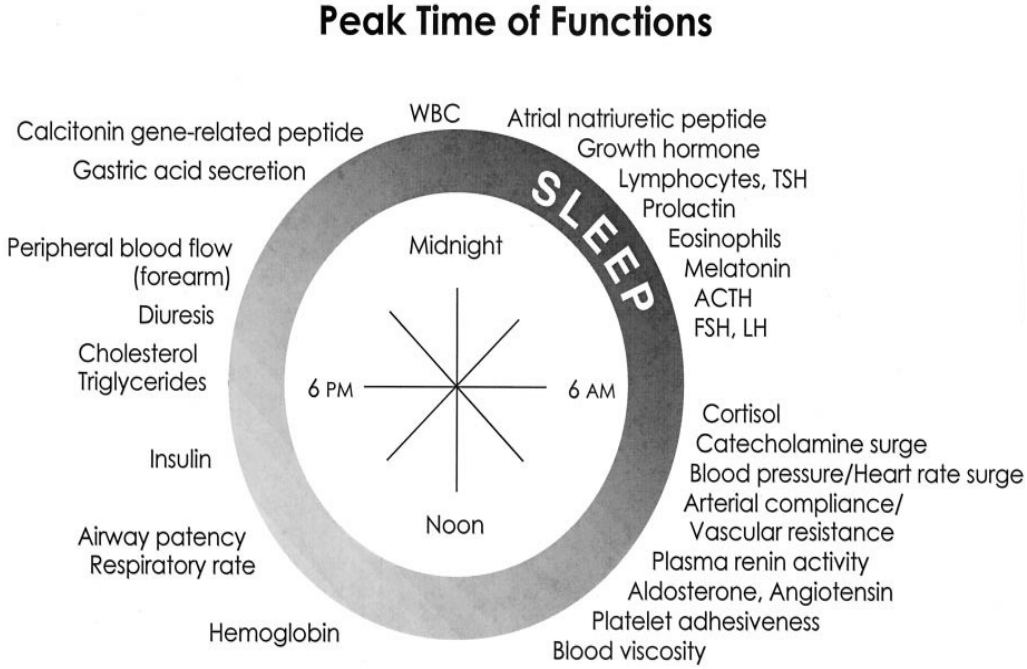


Fig.1 Biological clock shows circadian time structure of peak secretions and changes in our body.

ACTH = adrenocorticotropic hormone; FSH = follicle stimulating hormone;
LH = luteinizing hormone; TSH = thyroid stimulating hormone;
WBC = white blood cells.

2.2.1 Diagnostic tests: Circadian rhythm dependencies[1]

Several diagnostic tests are affected by circadian rhythms shown in Table 2.

Table 2 : Circadian rhythms: impact on the diagnosis of

medical conditions

Allergy: Cutaneous reaction to intradermal antigen tests two- to threefold greater in evening than in morning.
COPD: Airway patency best in the afternoon and poorest overnight. Morning best time to assess severity of asthma and differentiate between fixed and reversible airway disease.
Glaucoma: Intraocular pressure highest during sleep and lowest in afternoon. Early morning eye exams best for assessing at-risk patients; false-negative diagnosis more of a risk in the afternoon.
Circadian rhythm sleep disorders: Sleep phase delay syndrome (abnormally retarded sleep onset and offset times), sleep phase advanced syndrome (abnormally advanced sleep onset and offset times) and non–24-h sleep–wake syndrome (period of the sleep–wake cycle considerably different from 24 h) best diagnosed by wrist actigraphy.
Diabetes: Results of glucose tolerance test different in the morning than in afternoon, different times of the menstrual cycle, and different seasons of the year.
Laboratory chemistries: Plasma cortisol, melatonin, testosterone, and certain other hormone concentrations differ radically over the 24 h as do certain other commonly assessed blood constituents and parameters in hematology, such as the number of circulating granulocytes, lymphocytes, and their subtypes.
Blood pressure assessment: SBP and DBP rapidly rise in the morning by at least 15 to 25 mm Hg and reach highest levels late in the day. Typically SBP and DBP decline in sleep by 10% to 20% from daytime level. In uncomplicated essential hypertension, the pattern is similar, but the BP amplitude and/or 24-h mean abnormally elevated. In secondary hypertension, SBP and DBP may be normal or near normal in the day but abnormally high in sleep.

BP = blood pressure; COPD = chronic obstructive pulmonary

disease; DBP = diastolic blood pressure; SBP = systolic blood pressure.

2.2.2 Circadian rhythms of disease[3]

The symptom intensity of most medical conditions, including ones that involve the cardiovascular system, and occurrence of life-threatening medical emergencies exhibit rather precise timings (Fig. 2).

- Gout, gallbladder, and peptic ulcer attacks are most frequent at night.
- Acute pulmonary edema, congestive heart failure and asthma worsen nocturnally.
- Sudden infant death syndrome occurs most frequently in the middle of the night.
- Symptoms of allergic rhinitis and rheumatoid arthritis are most intense in the morning.
- Migraine headache typically is triggered during rapid eye movement (REM) episodes toward the end of nighttime sleep or early in the morning.
- Angina pectoris, acute myocardial infarction, sudden cardiac death, ventricular arrhythmia, stroke, fatal pulmonary embolism, and hypertensive crises are most frequent in the morning, as are certain other cardiovascular conditions.
- Depression is most severe in the morning.
- Symptoms of osteoarthritis worsen during the course of daily activity, usually being most bothersome in the evening.
- Perforated and bleeding ulcer is most common in the afternoon.
- Some seizure disorders are triggered in specific sleep stages and/or by transitions between sleep and wakefulness.

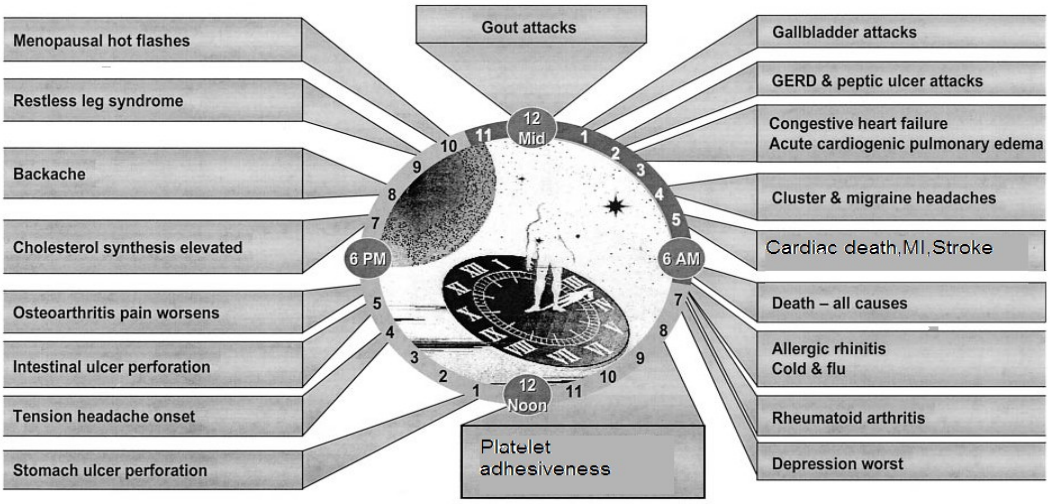


Fig. 2. Times when common medical conditions are likely to worsen and when morbid and mortal events are likely to occur with reference to the diurnal activity–nocturnal sleep routine of patients[4].

2.3 Circadian BP pattern[1]

The cardiovascular system, including blood pressure (BP) and heart rate (HR),are characterized by predictable changes during the 24 h, for the most part, in synchrony with the rest–activity cycle. The internal factors which influences the circadian BP are,

- Ethnicity,
- Gender,
- Autonomic nervous system tone,
- Vasoactive hormones,
- Hematologic variable, and Renal variable.

BP is also affected by a variety of external factors, including

- Ambient temperature/humidity,
- Physical activity,
- Emotional state,
- Alcohol/caffeine consumption,
- Meal composition, and Sleep/wake routine.

During the past two decades specific features of the 24-hour BP pattern have been assessed as potential sources of injury to target tissues and as triggers of cardiac and cerebrovascular events in hypertensive patients. Indeed, the prominent 24-hour variation in the occurrence of a variety of acute cardiovascular events, such as

Myocardial infarction, angina pectoris, cardiac arrest, sudden cardiac death, and pulmonary embolism, have been shown to be closely related to the circadian BP pattern of hypertensive subjects.

Indeed, the rate of rise of BP coincident with the commencement of diurnal activity has been identified as an independent predictor of one's risk of morning stroke and acute coronary syndrome, and it is also hypothesized to be a trigger for myocardial infarction at this time of day. Interestingly, some studies reveal the 24-hour pattern and, in particular, the characteristic morning peak in the occurrence of both ischemic and hemorrhagic stroke is the same in normotensive and hypertensive persons.

Collectively, all these observations strengthen the hypothesis that the morning surge in BP (in the presence or absence of systemic hypertension) is a crucial determinant of the rupture of a vulnerable and critically weakened arterial wall.

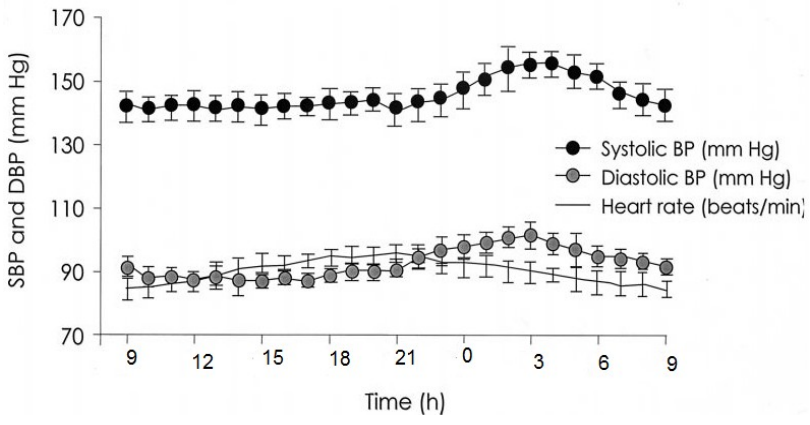


Fig.3. Circadian rhythm of systolic blood pressure (SBP) and diastolic blood pressure (DBP) in hypertensive persons

Circadian rhythm of systolic blood pressure (SBP) and diastolic blood pressure (DBP) in stage I essential hypertensive persons assessed by 24-h ambulatory blood pressure monitoring. Time along the X axis designates hours before and after waking from sleep. Note the rapid acceleration of BP at the commencement of the daily activity span.

A growing number of studies also indicate the extent of the nocturnal BP decline is deterministic of cardiovascular injury and risk. The recent VIIth report of the Joint National Committee states that

"Those individuals in whom a 10 to 20% decrease of BP during early morning is not present are at increased risk for cardiovascular events". The chronotherapy of hypertension takes into account the epidemiology of the circadian BP pattern, Specifically, it entails significant attenuation of the accelerated morning rise of systolic (SBP) and diastolic (DBP) BP, normalization of elevated daytime, nighttime, and 24-hour BP means, and conversion of an abnormal 24-hour BP profile, which is associated with reduced cardiovascular risk.

Chronotherapy antihypertensive medications. The pharmacotherapy of hypertension has been strongly influenced by the concept and assumptions of homeostasis. Until the last 10 or so years, the vast majority of the medical community believed SBP and DBP to be relatively constant throughout the 24 h. Consequently, it was deduced that a major goal of antihypertensive pharmacotherapy ought to be constancy of medication blood and tissue concentrations throughout the 24-hour dosing interval.

The chronotherapeutic perspective of 24-hour BP control entails the purposeful tailoring of medication level in close synchrony with the known (and expected) day–night pattern in SBP and DBP to optimize effect. Chronotherapeutic formulations rely on unique technologies to distribute this proportion of the daily dose to the time of day when BP rises to peak or near peak levels and when the greatest concentration of antihypertensive medications is required for BP control.

2.4 Biologic rhythms and medications[3]

Chronopharmacology the study of how biologic rhythms affect medications, has led to new understandings and concepts about the behavior of therapeutic agents.

Chronopathology is the study of biological rhythms in disease processes and in morbid and mortal events. Most medical conditions are affected by circadian rhythms. Cardiovascular diseases, which account for the greatest morbidity and mortality, are greatly affected by body rhythms. It is now generally recognized that myocardial infarctions, sudden cardiac death, transient ischemic attacks, and cerebrovascular accidents occur at a higher frequency in the early morning hours. In this issue, new information is provided in this evolving area of research.

Fig.4: Flowchart depicting a transition in therapeutics[3]

Chronokinetics : Refers to biologic rhythm effects on drug absorption, distribution, and elimination. Circadian changes in gastric hydrogen ion secretion, stomach emptying/ gastrointestinal transit time, liver enzyme activity, and organ blood flow, for example, can cause treatment time differences in the pharmacokinetics of medications. Chronokinetic phenomena may be specific to the chemical nature of the medication itself or to the physiochemical attributes of tablet, capsule, and aerosol drug-delivery technology. β-adrenergic receptor antagonists, theophylline, and nonsteroidal anti-inflammatory drugs (NSAID) are but a few examples of prescribed medications that show administration time (circadian rhythm) dependent differences in kinetics.

Chronesthesy*:* is another new concept in pharmacology. It refers to rhythm-dependent differences in the effects of medications that cannot be explained by their pharmacokinetics. Chronesthesies result from

rhythms in drugfree- fraction and rhythms in receptor number and conformation, second messenger dynamics, and rate-limiting steps of metabolic pathways in drug-targeted tissues.

Analgesics, anticoagulants, β-adrenergic receptor agonists and antagonists, corticosteroids, and NSAID are some examples of therapies that differ in effect according to their biologic time of administration.

***Chronotoxicity**:* Refers specifically to rhythm-dependencies in the manifestation and intensity of drug-related side effects. Medications that have a narrow therapeutic window and high risk of adverse effects (eg, NSAID, synthetic corticosteroids, and antitumor agents) commonly display significant circadian chronotoxicities.

Chronotherapeutics can also involve the application of physical agents. The successful management of certain conditions such as non–24-h sleep–wake disorder, seasonal affective disorder, and premenstrual dysphoric disorder, can be achieved by bright-light chronotherapy. The efficiency of radiotherapy for solid tumors is best when it is timed to coincide with the peak in tumor metabolism during the 24 h. The best known and most extensively used chronotherapy is the daily and alternate-day morning dosing schedule of corticosteroid medications. The principal goal of this treatment schedule is to ensure that the highest concentration of the synthetic hormone coincides in time with the morning peak of cortisol. In diurnally active individuals, this is when the hypothalamic-pituitary-adrenocortical axis is least vulnerable to suppression by exogenous corticosteroids. A list of other chronotherapies that are now in use in clinical medicine is presented in Table 3.

Table 3. Chronotherapies currently in clinical use[1]

- Once-daily and alternate-day morning corticosteroids dosing minimizes risk of adrenal suppression and other side effects.
- Bedtime corticosteroid dosing controls excessive hormone secretion in congenital adrenal hyperplasia.
- Asymmetrical morning high and late-afternoon low-dose corticosteroid substitution chronotherapy for Addison's disease best corrects fatigue and abnormal circadian time structure.
- Evening ingestion of certain HMG-CoA reductase antagonist medications optimizes cholesterol-lowering effect.
- Nitroglycerin transdermal patch medication worn during the portion of the 24 h to protect against angina when risk is greatest and removed in time to avoid sensitization to medication.
- Evening H2-receptor antagonist ingestion best controls nocturnal peptic ulcer and gastroesophageal reflux disease(GERD).
- Evening NSAID treatment optimizes attenuation of morning symptoms of rheumatoid arthritis; midday and/or afternoon NSAID treatment best for osteoarthritis that is typically worse in evening.
- Bedtime ADH analogue dosing helps to alleviate nocturnal bedwetting in children and nocturia in adults.
- Bedtime (but not morning) aspirin dosing best for preventing pregnancy-induced hypertension and preeclampsia.
- Evening theophylline chronotherapy (Uniphyl), producing highest drug concentration in sleep, optimizes control of nocturnal asthma and COPD.
- Evening verapamil chronotherapy (Verelan PM and Covera-HS) achieves more complete 24-h BP control than once-a-day conventional constant-release medications.
- Timed melatonin and bright-light chronotherapies enhance speed of

adjustment to alteration of the sleep–wake routine after rapid transmeridian displacement by airplane or rotation between day and night shifts.

- Timed bright-light chronotherapy is effective for seasonal affective disorder (SAD), premenstrual dysphoric disorder (PMDD), and circadian rhythm sleep disorders (advanced and delayed sleep phase syndromes and non–24-h sleep–wake cycle disorder).
- Luteal phase (commencing 6 to 14 days before menses) therapy of premenstrual dysphoric disorder (PMDD) using alprazolam, clomipramine, citalopram, fluoxetine, or sertraline.
- Infusion of cancer medications in synchrony with circadian rhythms minimizes drug-induced toxicity, enabling more aggressive treatment.

HMG-CoA =3-hydroxy-3methylglutaryl-coenzyme A; H2 = histamine type-2; NSAID = nonsteroidal anti-inflammatory drug; ADH =Antidiuretic hormone; COPD = chronic obstructive pulmonary disease.

Therapy with modified release dosage forms with zero order drug release theoretically leads to controlled and constant levels of drug in plasma throughout the day. However this does not provide extra therapeutic levels at the time of increased symptoms, and unwanted plasma drug concentration at other times of day may produce adverse effects with little therapeutic benefit. In order to optimize therapy in terms of safety, patient compliance and efficacy, chronopharmaceutical formulations based upon time controlled drug delivery systems (TCDDS) are considered to be potential therapeutic options. TCDDS are dosage forms that are designed to mimic the circadian rhythm of the disease by releasing the drug at the appropriate time.

2.5 Compression coated (or) Press coated tablets[6]

Tablet is defined as unit dose solid dosage form containing one or more drug with or without excipients having a definite pharmacological action.

The compressed tablets are made by more than one compression cycle. Recently a compression coated tablet has received increasing attention to deliver a drug in a pulsatile fashion rather than in a continuous way at predetermined times and/ or sites following oral administration.

This novel system not only rate controlled but time controlled to deliver the drug when it is required.

The compression coated tablet consists of an inner core and an outer coating shell. The outer coating material may be compressed on to the inner core with a special compression technique.

The manufacturing method of this tablet cannot only eliminate the time consuming and complicated operation processes but also improves the stability of drug by preventing it from moisture. To design a novel compression-coated tablet, the outer coating layer is critical in ensuring reliable tolerance to reach the predetermined site.

These are also referred to as dry-coated are prepared by feeding previously compressed tablet into a special tabletting machine and compressed another granulation layer around the preformed tablets.

2.5.1 Production of tablets

Tablets are made by compressing the formulation containing a drug or drugs with excipients on stamping machines called presses. Tablet compression machine or tablet presses are designed with the following basic components.

1. Hoppers for holding and feeding granulation to be compressed
2. Dies that define the size and shape of the tablet.
3. Punches for compressing the granulation within the dies.
4. Camtracks for guiding the movement of the punches.
5. A feeding mechanism for moving granulation from the hopper into the dies.

An example of a press-coated tabletting machine is the manesty drycota. Drycota : In 1937 killion , a german inventor received a british patent for a unit which compressed tablets on one machine and held them in the upper punches. These punches had rods passing lengthwise through them. The compression wheel was recessed so that it could compress the cores without activating the core rod. The cores were carried around the turret to the transfer mechanism. At this point the upper punches passed under a roller which pressed down the core rods, to the coating machine. It is evident that the drycota adopted the idea of two machines running synchronously from this patent.

2.5.2 Advantages of press coated tablets:

1. They have all the advantages of compressed tablets i.e. slotting, monogramming, speed of disintegration.
2. Masking the taste of the drug substance in the core tablets.
3. Used to separate incompatible drug substances.
4. Means of giving an enteric coating to the core tablets
5. Widely used in prolonged dosage forms.

2.6 Ideal characteristics of tablet dosage form[5]

- It has its own identity free of chips, cracks, discoloration and contamination.
- Should have strength to withstand vigorous mechanical shocks encounters in its production, packaging, shipping and dispensing.
- Should have chemical and physical stability.

On the other hand,

a. It must be able to release the medicinal agent in the body in a predictable and reproducible manner.

b. Must have a suitable chemical stability over time so as not to allow alterations of the medicinal agent.

c. Pre-compression of amorphous powders case negative effect on dissolution and disintegration rates.

2.7 Tabletting methods[7]

The three basic methods for the preparation of compressed tablets are

- Wet Granulation Method
- Dry Granulation Method or slugging method and
- Direct Compression

2.7.1 Direct compression

Direct compression consists of compressing tablets directly from powdered material without modifying the physical nature of the material itself. It involves only two operations, in sequence, powder mixing and tableting. The advantage of this is reduced cost production. The main

advantage of direct compression is it saves time when compared to other methods of compression like wet granulation.

Advantages of Direct Compression[7]

- The most obvious advantage is economy. Saving can occur in a number of areas including reducing process, time and thus reduced labour cost, fewer manufacturing steps and fewer equipments.
- Another advantage is in terms of tablet quality that is processing without the need of moisture and heat.
- Optimization of tablet disintegration in which each primary drug particle is liberated from tablet and available for dissolution.
- Fewer chemical stability problems would occur in direct compression.
- In direct compression, the disintegrant is able to perform optimally and when properly formulated, tablet made by direct compression should disintegrate rapidly to primary particles.

2.7.2 Requirements for directly compressible filler/binder are:

- High compactability to ensure that the compacted mass will remain bound after the release of the compaction pressure.
- Most directly compressible filler, binders undergo physical modification in order to improve tableting properties mainly compactability, flowabililty and apparent density.
- Good blending properties in order to avoid segregation.
- Most directly compressible materials are prepared by crystallization.

The crystal size and in part the crystal shape are selected by sieving (or) in some cases after grinding.

2.7.3 *Excipients used in direct compression:*

- ❖ Fillers – Spray dried lactose, Microcrystalline cellulose (MCC), Dicalcium phosphate, micro crystals of alpha monohydrate lactose.
- ❖ Disintegrating agent – direct compression starch, sodium carboxy methyl starch, cross linked carboxy methyl cellulose fibres, cross linked polyvinyl pyrrolidone.
- ❖ Lubricants – magnesim stearate, talc.
- ❖ Glidants – fumed silicon dioxide.

2.7.4 Factors to be considered for directly compressible excipients:

Flow ability:

Press speed requires powders to be very fluid, a property commonly referred to as product flow ability. Good flow characteristics are necessary because the mechanical action of the tablet press requires a volume of fill and this volume of fill represents the actual tablet weight. Thus the powders in the formula must possess a consistent particle-size distribution and density to attain proper flow and achieve volume of fill.

2.7.5 Compressibility:

Compressing a tablet of different powders that have varying physical characteristics can be difficult. If the formula has both characteristics like large particles with high moisture content and small dry particles then the tablet may or may not compress well and probably will have difficulty holding together.

Directly compressible materials are preprocessed or are found naturally in the granular state. The reduced number of processing steps required by directly compressible materials allows for less equipment and shorter process times in comparison with wet or dry granulation processes.

2.8 A systemic and modern approach to tablet product design[9]

Tablet product design requires two major activities. First, formulation activities begin by identifying the excipients most suited for a prototype formulation of the drug. Second, the levels of those excipients in the prototype formula must be optimally selected to satisfy all process/product quality constraints.

Factors affecting the type of excipients used in a tablet formula

The type of excipients used may vary depending on a number of preformulation, medical, marketing, economic and process/product quality factors as discussed in the following sections. Here we mainly focus on the process/product quality.

2.9 Typical tests performed on tablets are as follows:

- Weight variation
- Hardness
- Friability
- Disintegration time
- Dissolution
- Water content
- Content uniformity

Product quality is most often addressed at the tablet development stage. However, it is also important to monitor the processing quality of a formulation during development. They are:-

a. To optimize the process as well as the product.

b. To establish in-process quality control tests for routine production

It is more difficult to quantify the processing quality of a formulation than it is to measure the product quality. Some measurements that could be preformed on the process include:-

- Ejection force
- Capping
- Sticking
- Take-off force
- Flow of lubricated mixture
- Press speed (maximum)
- Frequency of weight control adjustments
- Sensitivity of formula to different presses
- Tooling wear
- Effect of consolidation load (Batch size)
- Hopper angle for acceptable flow
- Hopper orifice diameter for acceptable flow
- Compressional forces
- Environmental conditions (temperature, humidity and dust)

Each of the above processing parameters can become a source of trouble in scale-up (or) routine production. By monitoring these parameters in development, it may be possible to adjust the formula (or) process early enough to alleviate the source of trouble. The expected production output (number of tablets) per unit time will determine what speed tablet press will be required for a particular tablet product. If the anticipated unit output for a tablet product is expected to be large, a high-speed press will be required.

Attempts should be made in formulation development to design a tablet formula that will perform well on a high-speed press. A formula to run on a high-speed press should have excellent flow to maintain uniform die fill during compressing. It should have good bonding characteristics so that it can compress with a minimal dwell time.

2.10 Formulation of tablets and factors to be considered

The size and to some extent, the shape of the tablet are determined by the active ingredients. Drugs having very small doses in the microgram require the addition of fillers also called excipients to be added to produce a mass (or) volume of material that can be made into tablets of a size that is convenient for patients.

As the dose increases, so does the size of the table. Drugs with a dose of 100 to 200mg may require tablet weights of 150 to 300mg and round die diameters of 1/4 to 7/16 inches. The diameter depends on the density and compressibility of the powders used. As the dose of the active ingredient increases, the amount of the excipients and the size of the tablet may vary considerably depending on requirements of each to produce an acceptable tablet. While the diameter of the tablet may in some cases be fixed, the thickness is variable thus allowing the formulator considerable latitude and flexibility in adjusting formulations.

As the dose, and therefore the size of the tablet increases, the formulator uses his expertise and knowledge of excipients to keep the size of the tablet as small as possible without sacrificing its necessary attributes.

2.10.1 *Formulation of a tablet requires the following considerations:*

- Size of the dose (or) quantity of active ingredients
- Stability of active ingredients.
- Solubility of active ingredients.

- Density of active ingredients.
- Compressibility of active ingredients.
- Selection of excipients.
- Method of granulation (preparation for compression)
- Character of granulation
- Tablet press, type, size, capacity.
- Environmental conditions (ambient (or) humidity control)
- Stability of final product.
- Bioavailability of the active drug content of the tablet.
- The selection of excipients is critical in the formulation of tablets. Once the formulator has become familiar with the physical and chemical properties of the drug, the process of selecting excipients is begun. The stability of the drug should be determined with each proposed excipients. This can be accomplished as follows:

  In the laboratory, prepare an intimate mixture of the drug with an excess of each individual excipients and hold at 60˚C for 72hrs in a glass container. At the end of this period analyze for the drug using a stability-indicating assay.

2.10.2 Different adjuvants used in tablet formulation

In addition to the active or therapeutic ingredient, tablets contain a number of inert materials called as additives or excipients. Excipients are specified according to the function they perform in the tablet. They are classified as follows

- Fillers (Diluents)
- Glidants
- Lubricants

- Antiadherents, etc,

Diluents or Fillers[7]

These are the inert substances which will increase the bulk of tablet. Selecting the diluent is an important character while tabletting. These agents may not be necessary if the dose of drug per tablet is high. Generally, a tablet should weigh at least 100mg and therefore very low dose drugs will invariably require diluents to bring the overall tablet weight to atleast 100mg.

Diluents or fillers fall into two general categories:

1. Carbohydrate and modified carbohydrate excipients.
2. Inorganic materials

In wet granulation process, such carbohydrate substances as sugars, starches and cellulose may also function as binder. Where as in direct compression systems, they serve as diluent carrier. The inorganic excipients, when used in either system, are not binders that is a cohesive agent, in directly compressible system. Hence they function more as a carrier.

Microcrystalline cellulose: (MCC) (AVICEL) is most widely used as direct compression tablet filler. It has a function of disintegrant besides that of a dry binder and is compatible with most excipients and active ingredients.

Lactose is an inexpensive, soluble and easily granulated diluent. Because it lacks flowability and compressibility in its common form. Lactose in modified form can only be used in direct compression.

The other commonly used diluents are mannitol, kaolin, dry starch, calcium sulfate, dicalcium phosphate.

Glidants[1]

Glidants improve the flow characteristics of the powder mixture. These materials are added in the dry state just prior to compression. They

act by reducing the inter-particulate friction and reduce the frictional forces between the granules and dies. Colloidal silicon dioxide is the most commonly used glidant and generally used in low concentration of 1% or less. Talc is also used and may serve the dual purpose of glidant/ lubricant. It is important to optimize the order of addition and mixing process of these materials to maximize their effect and to make sure that their influence on lubricants is minimized.

Lubricants

They have a number of functions in tablet manufacture:-

- They prevent adhesion of the tablet material to the surface of the dies and punches
- Reduce interparticle friction
- Facilitate the ejection of tablets from the die cavity
- Improves the rate of flow of tablet granulation

Commonly used lubricants include talc, magnesium stearate, calcium stearate, stearic acid, hydrogenated vegetable oils. Most lubricants are used in concentration below 1% when used alone. Talc is used in concentration as high as 5%. Lubricants are mostly hydrophobic materials. Poor selection or excessive amounts can result in water proofing the tablets, resulting in poor tablet disintegration and / or delayed dissolution of drug substance.

Antiadherents

These are useful in tablet formulation, which have a tendency to pick easily. Multivitamin products containing high vitamin E levels often display extensive picking which can be minimized through the use of colloidal silica such as syloid (0.1-0.5%)

2.11 Controlled release tablets[11]

Conventional drug therapy typically involves the periodic dosing of a therapeutic agent that has been formulated in a manner to ensure its

stability, activity and bioavailability. For most of the drugs, conventional methods of formulation are quite effective. However some drugs are unstable, toxic and have narrow therapeutic range, exhibit extreme solubility problems, require localization to a particular site in the body or require strict compliance or long term use. In such cases a method of continuous administration of drug is desirable to maintain fixed plasma drug levels. The goal in designing sustained or controlled delivery is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery, so, controlled release dosage form is that release one or more drugs continuously in a predetermined pattern for a fixed period of time, either systemically or to a specified target organ. Controlled release dosage forms provide a better control of plasma drug levels, less dosage frequency, less side effect, increased efficacy and constant delivery.

2.11.1 Potential advantages of controlled drug therapy:[13]

All controlled release products share the common goal of improving drug therapy over achieved with their non-controlled counter parts. This improvement in drug therapy is represented by several potential advantages of the use of controlled release systems as mentioned below:

A) Avoid patient compliance problems.

B) Employ less total drug

- Minimize or eliminate local side effects.
- Minimize or eliminate systemic side effects.
- Obtain less potentiation or reduction in drug activity with chronic use.
- Minimize drug accumulation with chronic dosing

C) Improve efficiency in treatment

- Cure or control condition more promptly
- Improve control of condition i.e. reduce fluctuation in drug level.
- Improve bioavailability of some drugs.
- Make use of special effects e.g. sustained release aspirin for morning relief of arthritis by dosing before bedtime.
- Economy.

2.11.2 Limitations of oral CRDDS

On the other hand oral CRDDS suffer from a number of potential disadvantages:

- Relatively poor *in vitro-in vivo* correlation.
- Possible dose dumping
- Reduced potential for dose change or withdrawal in the event of toxicity
- Loss of effect due to diarrohea(too fast transit time)

2.12 Reasons for oral CRDDS

There is a clinical need to develop the CR formulations to improve the drug therapy over that achieved with their conventional counterparts, especially in the following cases:

I) Short elimination half life (t ½) and minimum effective concentration (MEC) required for the therapy. Shorter the half life of a drug, larger will be the fluctuations between the maximum steady state concentration (C^{SS}_{max}) and the minimum steady state concentration (C^{ss}_{min}) upon multiple dosing. If MEC is therapeutically required, either frequent dosing of a conventional drug product or development of a CR product is necessary.

II) Similarly the drugs having reasonably long elimination half- life and either wide or narrow therapeutic range. May also need to be formulated as CR products mainly for:

- Two to three day extension and
- Minimize the fluctuations between C^{SS}_{max} and C^{ss}_{min} with narrow therapeutic range drugs.

2.12.1 Drugs which are not ideal candidates for CR formulations

- Extensive first pass metabolism (except prodrugs)
- Extremely short elimination half-life (low therapeutic index)
- Extremely long elimination half-life (narrow therapeutic range)
- Bioavailability problems
- Instability in GI environment

2.12.2 An ideal candidate for CRDDS

The desired biopharmaceutic characteristics of drugs to be used in the development of per oral CR dosage forms are:

- Molecular weight: < 1000
- Solubility : > 0.1 mcg/ml at PH 1 to 7.8
- Non ionized moiety : > 0.1% to 11% at PH 1 to 7.8
- Apparent partition coefficient : 0.5 to 2.0
- General absorbability : from all GI segments
- Release should not be influenced by pH and enzymes
- Stability : stable in GI environment
- Less protein binding

To evaluate whether or not a drug is a viable candidate for the design of per oral CR formulations, one must consider the following pharmacokinetic parameters of the drug:

- Elimination half-life, t ½ : preferably between 0.5 to 8 hours
- Total clearance, CL : should not be dose dependant
- Elimination rate constant, K_{el} : required for the design
- Apparent volume of distribution, V_d the larger the V_d and MEC , the larger will be the required dose size. The maximum dose to be incorporates into a peroral CR formulations is about 500 mg. the smaller the V_d the easier is incorporation of drug into dosage form.
- Absolute bioavailability, F: should be 75% or more.
- Absorption rate, k_a : must be much greater than release rate
- Therapeutic concentration, C^{ss}_{av} : the lower the C^{ss}_{av} and the smaller the V_d, the lesser is the amount of drug required.
- Minimum toxic concentration, MTC: MTC and MEC, the further apart these two values are, the “safer” the dosage form and also suitable for drugs with very short half-life (t ½).

3. DRUG PROFILE

PROPRANOLOL HYDROCHLORIDE[17,19]

(β-adrenergic blocking agent)

Molecular Formula : $C_{16}H_{21}NO_2.HCl$

Molecular weight : 295.8

Indication : Adrenergic Non Selective β-receptor antagonist, which is used as Antihypertensive, Antianginal and Antiarrhythmic drug and it is used in the management of Myocardial infarction and Pheochromocytoma.

Chemical Name : (±)-1-Isopropylamino-3-(1-naphthyloxy) propan-2-ol hydrochloride.

Composition[14] : **C** (74.10%), **N** (5.40%), **H** (8.16%), **O** (12.34%)

Storage : Store in a well-closed container.

3.1 PHYSICAL AND CHEMICAL PROPERTIES[19]

Description	:	A white or off-white powder, odourless crystalline powder, bitter in taste.
Solubility	:	Soluble (1g dissolves in 10-30 ml) in water and ethanol. Slightly soluble in chloroform, practically insoluble in ether.
Dissociation constant	:	pk_a = 9.05
Partition coefficient	:	Log P (Octanol / water) = 2.75 – 2.65
pH	:	5.0 – 6.0, determined in 1% w/v solution
Polymorphism	:	Propranolol Hcl is known to have two polymorphic forms.
Colour Tests	:	Mandelin's Test-green; Marquis Test-green.
Infra-red spectrum	:	Principal peaks at wave numbers 1103, 1270, 772, 1580, 795, 1240 (Propranolol hydrochloride, KBr disc).

3.2 PHARMACOLOGICAL ACTION[18,21]

3.2.1 Cardiovascular

Propranolol diminishes heart rate, force of contraction and cardiac output, having both negative ionotropic and chronotropic effects. Cardiac output, work and oxygen consumption are decreased by blockade of β_1 receptors. These effects are useful in treatment of angina.

3.2.2 Peripheral vasoconstriction

Blockade of β receptors prevents β_2–mediated vasodialation. The reduction in cardiac output leads to decreased blood pressure. This hypotension triggers a reflex peripheral vasoconstriction that is reflected in reduced blood flow to the periphery.

3.2.3 Bronchoconstriction

Blocking β_2 receptors in lungs of susceptible patient causes contraction of the bronchiolar smooth muscle. This can precipitate a respiratory crisis in patients with chronic obstructive pulmonary disease or asthma. β-blockers are thus contraindicated in patient with asthma.

3.2.4 Increased sodium retention

Reduced blood pressure causes a decrease in renal perfusion, resulting in an increase in Na^+ retention and plasma volume.

3.2.5 Disturbance in glucose metabolism

β-blockade leads to decreased glycogenolysis and decreased glucagon secretion.

3.2.6 Blockade action of isoproterenol

Propranolol has the ability to block the actions of isoproterenol on cardiovascular system, so does not produce either the typical reduction in mean arterial pressure and diastolic pressure or cardiac stimulation.

3.3 THERAPEUTIC EFFECTS[21]

- **Hypertension:** Propranolol lowers blood pressure in hypertension by decreasing cardiac output.
- **Glaucoma:** Propranolol effectively diminishes intraocular pressure in glaucoma by decreasing the secretion of aqueous humor by the ciliary body.
- **Migraine:** Propranolol is effective in treatment of chronic migraine, in which the drug decreases the incidence and severity of the attacks.
- **Hyperthyroidism:** In acute hyperthyroidism (thyroid storm), β-blockers may be life saving in protecting against serious cardiac arrhythmias.

- **Angina Pectoris:** Propranolol decreases the oxygen requirement of heart muscle and therefore is effective in reducing the chest pain on execution that is common in angina. Therefore propranolol is useful in the chronic management of stable angina, but not for acute treatment.

- **Myocardial infarction:** Propranolol has a protective effect on the myocardium. It also reduces the incidence of sudden arrhythmic death after myocardial infarction.

3.4 ADVERSE EFFECTS[21]

- **Bronchoconstriction:** An immediate contraction of bronchiolar smooth muscle prevents air from entering the lungs. Death by asphyxiation has been reported, so propranolol must never be used in chronic obstructive pulmonary disease.

- **Arrhythmias:** Treatment with β-blockers must never be stopped quickly because of the risk of precipitating cardiac arrhythmias.

- **Sexual impairment:** Because sexual function in the male occurs through α-adrenergic activation, β-blockers do not affect normal ejaculation or the internal bladder sphincter function. On the other hand some men do complain of impaired sexual activity.

- **Disturbance in metabolism:** β-blockade leads to decreased glycogenolysis and decreased glucagon secretion. Fasting hypoglycemia may occur.

- **Drug interaction:** Drug that interferes with the metabolism of propranolol such as cimetidine, furosemide and chlorpromazine may potentiate its antihypertensive effects. Conversely that stimulate its metabolism, such as barbiturates, phenytoin and rifampacin, can mitigate its effects.

3.5 TOXICITY

Toxic effects have been associated with plasma concentration greater than 2 μg/ml and fatalities with concentration greater than 4μg/ml.

3.6 PHARMACOKINETIC PROPERTIES[20]

❖ Absorption

Propranolol is almost completely absorbed after oral administration (>90%) but undergoes extensive first-pass metabolism with considerable intersubject variation, bioavailability 10 to 50% (mean 30%).

Peak plasma concentration are reached with in 1-2 hour after oral administration of a single dose.

❖ Distribution

Propranolol is rapidly distributed over tissues. It is highly lipophilic and moderately bound to plasma proteins (80 – 95%) mainly to α-1 acid glycoprotein, volume of distribution (VOD) is about 4 liters/Kg. Propranolol is distributed into the lungs, liver, kidney, brain and heart.

❖ Metabolism & Excretion

Propranolol is almost completely metabolized in the liver. The main metabolites are naphthoxyl acetic acid (42%) 4- hydroxy Propranolol (41%) and Propranolol o-glucuronide (17%). 4- hydroxy Propranolol is pharmacologically active and is equipotent to the parent drug. However due to rapid conjugation the contribution to the pharmacological effect is low.

Elimination half-life is about 4 hours

Therapeutic concentration : In plasma, usually in the range 0.05 to 1μg/ml.

Clearance : Plasma clearance about 10 to 20 ml/min/kg.

Dose : 30 to 40mg of Propranolol hydrochloride daily.

3.7 CONTRA INDICATION[20]

Sinus bradycardia, cardiogenic shock, pulmonary oedema, severe hyperactive airway disease. compensated cardiac failure, Raynaud's disease, hypoglycemia, severe haemorrhage, 2nd or 3rd degree heart block.

3.8 INTERACTIONS

Decreased effect with aluminium and calcium salts, NSAIDS, ampicillin, rifampicin. Concurrent use of chlorpromazine results in raised blood levels of additive hypotensive effect. Hypotensive effect reduced by indomethacin. Plasma levels may be increased by Hydralazine.

3.9 ADR[15]

Cold extremities, insomnia, fatigue, dizziness, vivid dreams, lassitude, nausea, constipation (or) diarrhea, impotence, wheezing, bronchospasm.

4. POLYMER PROFILE[22]

4.1 ETHYL CELLULOSE

Nonproprietary names

BP : Ethylcellulose

PhEur : Ethylcellulosum

USPNF : Ethylcellulose

Synonyms: Aqua coat ECD; Aqualon; E462; Ethocel; Surelease.

Chemical name and CAS registry number

Cellulose ethyl ether [9004-57-3]

Empirical formula & molecular weight

Ethylcellulose with complete substitution (DS=3) is $C_{12}H_{23}O_6$ $(C_{12}H_{22}O_5)_n$ $C_{12}H_{23}O_5$ where n can vary to provide a wide variety of molecular weights. Ethylcellulose, and ethyl ether of cellulose, is a long-chain polymer of β–anhydroglucose units jointed together by acetal linkages.

Functional category

Coating agent; flavoring fixative; tablet binder; tablet filler; viscosity–increasing agent.

4.1.1 Applications in pharmaceutical formulation or technology

Ethylcellulose is widely used in oral and topical pharmaceutical formulations; see Table 4.

The main use of ethylcellulose in oral formulations is as a hydrophobic coating agent for tablets and granules. Ethylcellulose coatings are used to modify the release to a drug to mask an unpleasant

taste, or to improve the stability of a formulation; for example, where granules are coated with ethylcellulose to inhibit oxidation. Modified – release tablet formulations may also be produced using ethylcellulose as a matrix former.

Ethylcellulose, dissolved in an organic solvent or solvent mixture, can be used on its own to produce water – insoluble films. Higher – viscosity ethylcellulose grades tend to produce stronger and more durable films. Ethylcellulose films may be modified to alter their solubility by the addition of hypromellose or a plasticizer. An aqueous polymer dispersion (or latex) of ethylcellulose such as Aquacoat ECD (FMC Biopolymer) or Surelease (Colorcon) may also be used to produce ethylcellulose films without the need for organic solvents.

Drug release through ethylcellulose coated dosage forms can be controlled by diffusion through the film coating. This can be a slow process unless a large surface area (e.g. pellets or granules compared with tablets) is utilized. In those instances, aqueous ethylcellulose dispersions are generally used to coat granules or pellets. Ethylcellulose-coated beads and granules have also demonstrated the ability to absorb pressure and hence protect the coating from fracture during compression.

High-viscosity grades of ethylcellulose are used in drug microencapsulation. Release of a drug from an ethylcellulose microcapsule is a function of the microcapsule wall thickness and surface area. In tablet formulations, ethylcellulose may additionally be employed as a binder; the ethylcellulose may additionally be wet-granulated with a solvent such as ethanol (95%). Ethylcellulose produces hard tablets with low friability, although they may demonstrate poor dissolution.

Ethylcellulose has also been used as an agent for delivering therapeutic agents from oral (e.g., dental) appliances. In topical formulations, Ethylcellulose is used as a thickening agent in creams, lotions, or gels, provided an appropriate solvent is used. Ethylcellulose is

additionally used in cosmetics and food products.

Table 4: Uses of Ethylcellulose

Use	Concentration (%)
Microencapsulation	10.0-20.0
Sustained – release tablet coating	3.0-20.0
Tablet coating	1.0-3.0
Tablet granulation	1.0-30.0

Description

Ethylcellulose is a tasteless, free- flowing, white or light tan-colored powder.

4.1.2 Typical properties

Density (bulk) **:** 0.4g/cm ^{3}

Glass transition temperature **:** 129-133℃

Moisture content:

Ethylcellulose absorbs very little water from humid air or during immersion, and that small amount evaporates

***Solubility*:**

Ethylcellulose is practically insoluble in glycerin, propylene glycol, and water. Ethylcellulose that contains less than 46.5% of ethoxyl groups is freely soluble in chloroform, methyl acetate, and tetrahydrofuran, and in mixtures of aromatic hydrocarbons with ethanol (95%). Ethylcellulose that contains not less than 46.5% of ethoxyl acetate, methanol and toluene.

Specific gravity: 1.12-1.15 g/cm^3

Viscosity: The viscosity of ethylcellulose is measured typically at 25°C using 5% w/v ethylcellulose dissolved in a solvent blend of 80% toluene: 20% ethanol

(w/w). Grades of ethylcellulose with various viscosities are commercially available; see Table III. They may be used to produce 5% w/v solutions in organic solvent blends with viscosities normally ranging from 7 to 100 mPas (7-100 cp). Specific ethylcellulose grades, or blends of different grades, may be used to obtain solutions of a desired viscosity. Solutions of higher viscosity tend to be composed of longer polymer chains and produce strong and durable films.

4.1.3 Stability and storage conditions:

Ethylcellulose is a stable, slightly hygroscopic material. It is chemically resistant to alkalis, both dilute and concentrated and to salt solutions, although it is more sensitive to acidic materials than are cellulose esters.

Ethylcellulose is subject to oxidative degradation in the presence of sunlight or UV light at elevated temperatures. This may be prevented by the use of antioxidant and chemical additives that absorb light in the 230-340 nm range.

Ethylcellulose should be stored at a temperature not exceeding 32℃ (90℉) in a dry area away from all sources of heat. It should not be stored next to peroxides or other oxidizing agents.

Incompatibilities:

Incompatible with paraffin wax and microcrystalline wax.

4.1.4. Safety:

Ethylcellulose is widely used in oral and topical pharmaceutical formulations. It is also used in food products. Ethylcellulose is not metabolized following oral consumption and is therefore a noncalorific substance. Because ethycellulose is not metabolized it is not recommended for parenteral products; paranteral use may be harmful to the kidneys.

Ethylcellulose is generally regarded to be a health hazard; the WHO has not specified an acceptable daily intake.

- LD_{50} (rabbit, skin): >5 g/kg (28)
- LD_{50} (rat,oral): >5 g/kg

Handling precautions:

It is important to prevent fine dust clouds of ethylcellulose from reaching potentially explosive levels in the air. Ethylcellulose is combustible. Ethylcellulose powder may be an irritant to the eyes and eye protection should be worn.

4.2 XANTHAN GUM

Non proprietary names:

- BP : Xanthan gum
- PhEur : Xanthani gummi
- USPNF : Xanthan gum

Synonyms: Corn sugar gum; E415; Keltrol; polysaccharide B-1459; Rhodigel; Vanzan NF; Xantural.

Chemical name and CAS Registry number

Xanthan gum [11138-66-2]

Empirical formula:

The USPNF 20 describes xanthan gum as a high molecular weight polysaccharide gum. It contains D-glucose and D-mannose as the dominant hexose units, along with D-glucuronic acid.

The molecular weight is approximately 2×10^6

Structural formula:

Each xanthan gum repeat unit contains five sugar residues: two glucose, two mannose and one glucuronic acid. The polymer backbone consists of four β-

D-glucose units linked at the 1 and 4 positions and is therefore identical in structure to cellulose. Each side chain comprises a glucuronic acid residue between two mannose units. At most of the terminal mannose units is a pyruvate moiety; the resulting stiff polymer chain may exist in solution as a single, double, or triple helix that interacts with other xanthan gum molecules to form complex, loosely bound networks.

Functional category:

Stabilizing agent; suspending agent; viscosity-increasing agent.

4.2.1 Application in pharmaceutical formulation or technology[22]

Xanthan gum is widely used in oral and topical pharmaceutical formulations, cosmetics and foods as a suspending and stabilizing agent. It is also used as a thickening and emulsifying agent. It is nontoxic, compatible with most other pharmaceutical ingredients and has good stability and viscosity properties over a wide pH and temperature range.

When xanthan gum is mixed with certain inorganic suspending agents, such as magnesium aluminum silicate or organic gums, synergistic rheological effects occur. In general mixtures of xanthan gum and magnesium aluminum silicate in ratios between 1:2 and 1:9 produce the optimum properties. Similarly, optimum synergistic effects are obtained with xanthan gum : guar gum ratios between 3:7 and 1:9.

Although primarily used as a suspending agent, xanthan gum has also been used to prepare sustained-release matrix tablets.

Xanthan gum is also used as a hydrocolloid in the food industry and in cosmetics it has been used as a thickening agent in shampoo.

Description: Xanthan gum occurs as a cream or white colored, odorless, free-flowing, fine powder.

4.2.2 Typical properties

Acidity/alkalinity : **pH** = 6.0-8.0 for a 1% w/v aqueous solution.

Freezing point : 0°C for a 1% w/v aqueous solution.

Heat of combustion : 14.6 J/g (3.5cal/g)

Melting point : Chars at 270°C.

Particle size distribution:

various grades with different particle sizes are available; for example, 100% less than 180μm in size for Keltrol CG; 100% less than 75 μm in size for Keltrol CGF;100% less than 250 μm, 95% less than 177 μm in size for Rhodigel;100% less than 177 μm 92% less than 74 μm in size for Rhodigel 200.

Refractive index: : 1.333 for a 1% w/v aqueous solution.

Solubility : Practically insoluble in ethanol and ether; soluble in cold or warm water.

Specific gravity : 1.600 at 25°C

Viscosity (dynamic) : 200-1600 mPas (1200-1600 cP) for a 1% w/v aqueous solution at 25°C.

4.2.3 Stability and storage conditions

Xanthan gum is a stable material. Aqueous solutions are stable over a wide pH range of 3-12. Although they demonstrate maximum stability at pH 4-10 and temperatures of 10-60°C. Xanthan gum solutions of less than 1% w/v concentration may be adversely affected by higher than ambient temperatures: for example, viscosity is reduced. Solutions are also stable in the presence of enzymes, salts, acids and bases.

The bulk material should be stored in a well-closed container in a cool, dry place.

4.2.4 Incompatibilities

Xanthan gum is an anionic material and is not usually compatible with cationic surfactants, polymers, or preservatives as precipitation occurs. Anionic and amphoteric surfactants at concentrations above 15% w/v cause precipitation of xanthan gum from a solution.

Xanthan gum is incompatible with oxidizing agents, some tablet film-coatings, carboxymethylcellulose sodium, dried aluminum hydroxide gel, and some active ingredients such as amitriptyline, tamoxifen and verapamil.

Method of manufacture

Xanthan gum is a polysaccharide produced by a pure-culture aerobic fermentation of a carbohydrate with Xanthomonas campestris. The polysaccharide is then purified by recovery with propan-2-ol, dried and milled.

4.2.5 Safety

Xanthan gum is widely used in oral and topical pharmaceutical formulations, cosmetics and food products and is generally regarded as non toxic and nonirritant at the levels employed as a pharmaceutical excipient.

The estimated acceptable daily intake for xanthan gum has been set by the WHO at upto 10 mg/kg body-weight.

Handling precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended.

Regulatory status

GRAS listed accepted for use as a food additive in Europe. Included in the FDA inactive ingredients guide (oral solutions, suspensions and tablets; rectal and topical preparations). Included in nonparenteral medicines licensed in the UK.

4.3 GUAR GUM

Non proprietary names:

BP :Guar galactomannan

PhEur : Guar galactomannum

USPNF:Guar gum

Synonyms: E412; Galactosol; guar flour; jaguar gum; meprogat; meprodor; meyprofin; meyproguar.

Chemical name and CAS Registry number:

Galactomannan polysaccharide [9000-30-0]

Empirical formula: $(C_6H_{12}O_6)n$

Molecular weight : 220000

Structural formula:

Guar gum consists of linear chains of (1→4)-β-D-mannopyranosyl units with α-D-galactopyranosyl units attached by (1→6) linkages. The ratio of D-galactose to D-mannose is between 1:1.4 and 1:2

Functional category

Suspending agent; tablet binder; tablet disintegrant; viscosity-increasing agent.

4.3.1 Application in pharmaceutical formulation or technology[22]

Guar gum is a galactomannan, commonly used in cosmetics, food products and pharmaceutical formulations. It has also been investigated in the preparation of sustained-release matrix tablets in the place of cellulose derivatives such as methyl cellulose.

In pharmaceuticals, guar gum is used in solid-dosage forms as a binder and disintegrant and in oral and topical products as a suspending, thickening and stabilizing agent and also as a controlled-release carrier. Guar gum has also been examined for use in colonic drug delivery.

Therapeutically, guar gum has been used as part of the diet of patients with diabetes mellitus. It has also been used as an appetite suppressant.

Table 5: Uses of guar gum

Use	Concentration (%)
Emulsion stabilizer	1%
Tablet binder	Up to 10%
Thickener for lotions and creams	Up to 2.5%

4.3.2 Description

The USPNF 20 describes guar gum as a gum obtained from the ground endosperms of Cyamopsis tetragonolobus (L.) Taub. (fam. Leguminosae). It consists chiefly of a high-molecular weight hydrocolloidal polysaccharide, composed of galactan and mannan units combined through glycoside linkages, which may be described chemically as a galactomannan.

The main components are polysaccharides composed of D-galactose and D-mannose in molecular ratios of 1:1.4 to 1:2. The molecule consists of a linear chain of β - (1→4)- glycosidically linked manno-

pyranoses and single α-(1→6)- glycosidically linked galacto-pyranoses.

Guar gum occurs as an odorless, white to yellowish-white powder with a bland taste.

Typical properties

Acidity/alkalinity: pH = 5.0-7.0 (1% w/v aqueous dispersion)

Density : 1.492 g/cm^3

Solubility:

Practically insoluble in organic solvents. In cold or hot water, guar gum disperses and swells almost immediately to form a highly viscous, thixotropic sol. The optimum rate of hydration occurs at pH 7.5-9.0. Finely milled powders swell more rapidly and are more difficult to disperse. Two to four hours in water at room temperature are required to develop maximum viscosity.

Viscosity (dynamic):

4.86 Pas (4860cP) for a 1% w/v dispersion. Viscosity is dependent upon temperature, time, concentration, pH, rate of agitation and particle size of the guar gum. Synergistic rheological effects may occur with other suspending agents such as xanthan gum.

4.3.3 Stability and storage conditions

Aqueous guar gum dispersions have a buffering action and are stable between pH 4.0 and 10.5. however, prolonged heating reduces the viscosity of dispersions.

The bacteriological stability of guar gum dispersions may be improved by the addition of a mixture of 0.15% methyl paraben and 0.02%

propyl paraben as a preservative. In food applications, benzoic acid, citric acid, sodium benzoate or sorbic acid may be used. Guar gum powder should be stored in a well-closed container in a cool, dry place.

Incompatibilities

Guar gum is compatible with most other plant hydrocolloids such as tragacanth. It is incompatible with acetone, alcohol, tannins, strong acids and alkalis. Borate ions, if present in the dispersing water, will prevent the hydration of guar gum. However, the addition of borate ions to hydrated guar gum produces cohesive structural gels and further hydration is then prevented. The gel formed can be liquefied by reducing the pH to below 7 or by heating. Guar gum may reduce the absorption of penicillin V from some formulations by a quarter.

4.3.4 Method of manufacture

Guar gum is obtained from the ground endosperm of the guar plant, Cyamopsis tetragonolobus (L.) Taub. (Fam. Leguminosae) which is grown in India, Pakistan and southwest region of the USA.

The seed hull can be removed by grinding, after soaking in sulfuric acid or water or by charring. The embryo (germ) is removed by differential grinding, since each component possesses a different hardness. The separated endosperm, containing 80% galactomannan is then ground to different particle sizes depending upon final application.

Safety

Guar gum is widely used in foods and oral and topical pharmaceutical formulations. Excessive consumption may cause gastrointestinal disturbance such as flatulence, diarrhea or nausea. Therapeutically, daily oral doses of up to 25g of guar gum have been administered to patients with diabetes mellitus.

Although it is generally regarded as a nontoxic and non-irritant material, the safety of guar gum when used as an appetite suppressant has been questioned. When consumed, the gum swells in the stomach to

promote a feeling of fullness. However, it is claimed that premature swelling of guar gum tablets may occur and cause obstruction of or damage to the oesophagus. Consequently, appetite suppressants containing guar gum in tablet form have been banned in the UK. However, appetite suppressants containing microgranules of guar gum are claimed to be safe. The use of guar gum for pharmaceutical purposes is unaffected by the ban.

In food applications, an acceptable daily intake of guar gum has not been specified by the WHO.

LD_{50} (rabbit, oral):7.0 g/kg

LD_{50} (rat,oral): 6.77 g/kg

4.3.5 Handling precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Guar gum may be irritating to the eyes. Eye protection, gloves and a dust mask or respirator are recommended.

Regulatory status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA inactive ingredients guide (oral suspensions, syrups and tablets). Also included in nonparenteral medicines licensed in the UK.

Comments

Synthetic derivatives of guar gum such as guar acetate, guar phthalate, guar acetate phthalate, oxidized guar gum and sodium carboxymethyl guar gum have also been investigated for their pharmaceutical applications. In particular sodium carboxymethyl guar gum gives a transparent gel and when poured over a pool of mercury, produces a flexible, clear, transparent film. sodium carboxymethyl guar gum has been used as a polymer matrix in transdermal patches.

4.4 HYPROMELLOSE

Nonproprietary names

BP: Hypromellose

JP: Hydroxypropylmethylcellulose

PhEur: Hypromellosum

USP: Hypromellose

Synonyms

Benecel MHPC; hydroxypropyl methyl ether; E464; hydroxypropyl methylcellulose; HPMC; Methocel; methylcellulose propylene glycol ether; merthyl hydroxypropylcellulose; Metolose ; Pharmacoat ; Spectracel 6 ; Spectracel 15; Tylopur.

Chemical name and CAS registry number

Cellulose, 2-hydroxypropyl-methyl ether [9004-65-3]

Empirical formula molecular weight

The PhEur 2002 describes hypromellose as a partly O-methylated and O-(2-hydroxypropylated) cellulose. It is available in several grades that vary in viscosity and extent of substitution. Grades may be distinguished by appending a number indicative of the apparent viscosity, in mPa s, of a 2% w/w aqueous solution at 20℃. Hypromellose defined in the USP 25 specifies the substitution type by appending a four-digit number to the nonproprietary name: e.g., hypromellose 1828. The first two digits refer to the approximate percentage content of the methoxy group (OCH3). The second two digits refer to the approximate percentage content of the methoxy group (OCH3). The second two digits refer to the approximate percentage content of the hydroxypropoxy group (OCH2CH (OH) CH3), calculated on a dried basis. Molecular weight is approximately 10 000-1 500 000. The Jp 2001 includes three separate monographs for hypromellose: hydroxypropylmethylcellulose 2208, 2906, and 2910, respectively.

Functional category

Coating agent; film-former; rate – controlling polymer for sustained release; stabilizing agent; suspending agent; tablet binder; viscosity – increasing agent.

4.4.1 Applications in pharmaceutical formulation or technology[22]

Hypromellose is widely used in oral and topical pharmaceutions, Particularly ophthalmic preparations. Compared with methylcellulose, hypromellose produces solutions of greater clarity, with fewer undispersed fibers present, and is therefore preferred in formulations for ophthalmic use. Hypromellose at concentrations between 0.45-1.0% w/w may be added as a thickening agent to vehicles for eye drops and artificial tear solutions.

Hypromellose is also used as an emulsifier, suspending agent, and stabilizing agent in topical gels and ointments. As a protective colloid, it can prevent droplets and particles from coalescing or agglomerating, thus inhibiting the formation of sediments.

In addition, hypromellose is used in the manufacture of capsules, as an adhesive in plastic bandages, and as a wetting agent for hard contact lenses. It is also widely used in cosmetics and food products.

Description

Hypromellose is an odorless and tasteless, white or creamy white fibrous or granular powder.

4.4.2 Typical properties

Acidity / alkalinity: pH = 5.5 – 8.0 for a 1% w/w aqueous solution

Ash: 1.5-3.0% depending upon the grade

Autoignition temperature: 360℃

Density (tapped): 0.557 g/cm^3

Density (tapped): 1.326 g/cm^3

Melting point: browns at 190-200℃; chars at 225-230℃.

Glass transition temperature is 170-180℃.

Moisture content:

Hypromellose absorbs moisture from the atmosphere, the amount of water absorbed depending and relative humidity of the surrounding air.

Solubility:

Soluble in cold water, forming a viscous colloidal solution; practically insoluble in chloroform, ethanol (95%), and ether, but soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and dichloromethane, and mixtures of water and alcohol. Certain grades of hypromellose are soluble in aqueous acetone solutions, mixtures of dichloromethane and propan-2-ol, and other organic solvents.

Specific gravity: 1.26

4.4.3 Viscosity (dynamic):

Wide ranges of viscosity types are commercially available. Aqueous solutions are most commonly prepared, although hypromellose may also be dissolved in aqueous alcohols such as ethanol and propan-2-ol provided the alcohol content is less than 50% w/w. Dichloromethane and ethanol mixtures may also be used to prepare viscous hypromellose solutions. Solutions prepared using organic solvents tend to be more viscous; increasing concentration also produces more viscous solutions.

HPMC grade	Nominal	Viscosity (mPa s)
K 100LVP	100	80-120
K4M	4000	3000-5600
K15M	15000	12000-21000
K100M	100 000	80 000-120 000

To prepare an aqueous solution, it is recommended that hypromellose is dispersed and thoroughly hydrated in about 20-30% of the required amount of water. The water should be vigorously stirred and heated to 80-90℃, then the remaining hypromellose added. Cold water should then be added to produce the required volume.

When a water miscible organic solvent such as ethanol, glycol, or mixtures of ethanol and dichloromethane is used, the hypromellose should first be dispersed into the organic solvent, at a ratio of 5-8 parts of solvent to part of hypromellose. Cold water is then added to produce the required volume.

4.4.4. Stability and storage conditions

Hypromellose powder is a stable material, although it is hygroscopic after drying. Solutions are stable at pH 3-11. Increasing temperature reduces the viscosity of solutions. Hypromellose undergoes a reversible sol-gel transformation upon heating and cooling, respectively. The gel point is 80-90℃, depending upon the grade and concentration of material. Hypromellose powder should be stored in a well-closed container, in a cool, dry place.

Incompatibilities

Hypromellose is incompatible with some oxidizing agents. Since it is nonionic, hypromellose will not complex with metallic salts or ionic organics to form insoluble precipitates.

Safety

Hypromellose is widely used as an excipient in oral and topical pharmaceutical formulations. It is also used extensively in cosmetics and food products.

Hypromellose is generally regarded as a nontoxic and nonirritant material, although excessive oral consumption may have a laxative effect. The WHO has not specified an acceptable daily intake fro hypromellose since the levels consumed were not considered to represent a hazard to health.

LD_{50} (mouse, IP): 5 g/kg (16)

LD_{50} (rat, IP): 5.2 g/kg

Handling precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Hypromellose dust may be irritant to the eyes and eye protection is recommended. Excessive dust generation should be avoided to minimize the risks of explosion. Hypromellose is combustible.

4.5 CELLULOSE, MICROCRYSTALLINE

Nonproprietary names

BP: Microcrystalline cellulose

JP: Microcrystalline cellulose

PhEur: Cellulosum microcristallinum

USPNF: Microcrystalline cellulose

Synonyms

Avicel PH; Celex; cellulose gel; Celphere; Ceolus KG; crystalline cellulose; E460; Emcocel; Ethispheres; *Fibrocel*; Pharmacel; *Tabulose*; Vivapur.

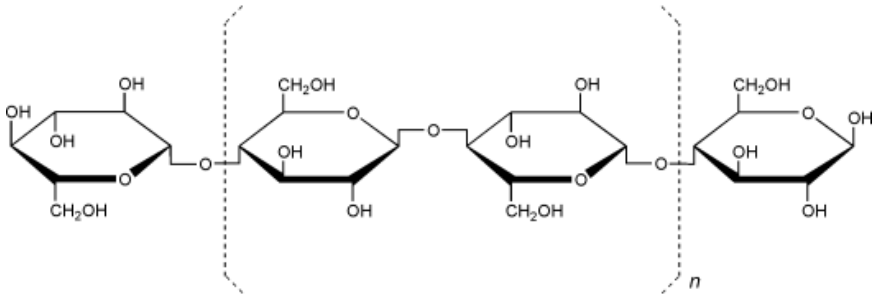
Chemical name and CAS Registry number

Cellulose [9004-34-6]

Empirical formula and molecular weight

$(C_6H_{10}O_5)_n$ ≈36 000. where $n \approx 220$.

Structural Formula



Functional Category

Adsorbent; Suspending agent; Tablet and Capsule Diluent; Tablet Disintegrant.

4.5.1 Applications in pharmaceutical formulation or technology[22]

Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct-compression processes. In addition to its use as a binder/diluent, microcrystalline cellulose also has some lubricant and disintegrant properties that make it useful in tableting. Microcrystalline cellulose is also used in cosmetics and food products; *see* Table 6.

Table 6: Uses of microcrystalline cellulose

Use	Concentration (%)
Adsorbent	20–90
Antiadherent	5–20
Capsule binder/diluent	20–90
Tablet disintegrant	5–15
Tablet binder/diluent	20–90

Description

Microcrystalline cellulose is a purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grades that have different properties and applications.

4.5.2 Typical properties

Solubility: *Slightly soluble in 5% w/v sodium hydroxide solution; practically insoluble in water, dilute acids, and most organic solvents.*

Stability and storage conditions

Microcrystalline cellulose is a stable though hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry place.

Incompatibilities

Microcrystalline cellulose is incompatible with strong oxidizing agents.

4.5.3 Safety

Microcrystalline cellulose is widely used in oral pharmaceutical formulations and

food products and is generally regarded as a relatively nontoxic and nonirritant material. Microcrystalline cellulose is not absorbed systemically following oral administration and thus has little toxic potential. Consumption of large quantities of cellulose may have a laxative effect, although this is unlikely to be a problem when cellulose is used as an excipient in pharmaceutical formulations. Deliberate abuse of formulations containing cellulose, either by inhalation or by injection, has resulted in the formation of cellulose granulomas.

Handling precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Microcrystalline cellulose may be irritant to the eyes. Gloves, eye protection, and a dust mask are recommended. In the UK, the occupational exposure limits for cellulose have been set at 10 mg/m^3 long-term (8-hour TWA) for total inhalable dust and 4 mg/m^3 for respirable dust; the short-term limit for total inhalable dust has been set at 20 mg/m^3.

5. LITERATURE REVIEW

5.1 **Veena S Belgamwar**, **Madhura V Gaikwad, *et al.*,[23] 2009**, Developed and evaluated Pulsatile drug delivery system designed for chronopharmcotherapy which is based on circadian rhythm. Pulsatile drug delivery system is defined as the rapid and transient release of certain amount of molecules with in a short period immediately after a predetermined off-release period i.e. lag time. It consists of capsule or tablet composed of large number of pellets. Each pellets has a core that contain therapeutic drug and a water soluble osmotic agent (e.g., Nacl). The osmotic agent dissolves in water, which causes the pellets to swell & there by regulates the rate of diffusion of drug from the dosage form.

5.2 **Usha Yogendra Nayak**, **Gopal Venktesh Shavi, *et al.*,[24] 2009**, developed a pulsatile capsule dosage form of valsartan for controlled delivery. In the majority of individuals blood pressure rises in the early morning hours, which lead to serious cardiovascular complications. The prepared system contained swellable polymer (L-hydroxypropyl cellulose (L-HPC), xanthan gum, polyethylene oxide or sodium alginate) together with drug tablet and erodible tablet (L-HPC or guar gum) in a pre-coated capsule. The formulation containing 200 mg sodium alginate and erodible tablet (150 mg) containing 50% guar gum and 46% lactose showed 5–6 h lag time and 10±2.1% drug release in initial 6 h following rapid release (99±1.7% release in 12 h) of drug was observed. Thus this approach can provide a useful means for timed release of valsartan and may be helpful for patients with morning surge.

5.3 **Yasser El-Malah, Sami Nazzal *et al.,*[25] 2008**, studied on Novel use of Eudragit NE 30D/Eudragit L 30D-55 blends as functional coating materials in time-delayed drug release applications. It is formulated by Eudragit NE 30D and L 30D-55 dispersions were blended at 50:50, 67:33, 75:25, and 80:20 ratios. Cast films were evaluated by texture analysis and differential scanning colorimetry. Increasing Eudragit NE 30D concentration increased miscibility, softness, and decreased stiffness of the films. At 80:20 ratio, the polymer blend was completely miscible whereby Eudragit L 30D-55 was molecularly distributed in the mixture. This was confirmed by SEM analysis. A lag time could therefore be controlled by manipulating both the theoretical weight gain of the beads and the concentration of Eudragit NE 30D in the blend.

5.4 **Qureshi.J, Mohd, Amir Alka Ahuja, *et al.,*[26] 2008**, Chronomodulated drug delivery system of Salbutamol sulphate for the treatment of Nocturnal Asthma. It consists of an effervescent core surrounded by consecutive layers of swelling and rupturable polymers. The core containing salbutamol sulphate & different ratios of MCC & effervescent agent and then coated with an inner Swelling layer containing HPMC E5 and an outer rupturable layer having Eudragit RL/RS (1:1). The rupture & dissolution tests were studied using the USP paddle method at 50 rpm in 0.1 N Hcl &phosphate buffer pH 6.8. The lag time of the drug release decreased by increasing the inner swelling layer and increased by increasing the rupturing layer level.

5.5 **Ramón C. Hermida**, **Diana E. Ayala, *et al.,*[2] 2007**, studied on Chronotherapy of hypertension: valsartan administration at bedtime, as opposed to upon wakening, results in an improved diurnal/nocturnal BP ratio, increased percentage of controlled patients, and significant reduction in urinary albumin excretion in

hypertensive patients. Chronotherapy provides a new option to optimize BP control and to reduce the risk of cardiovascular disease (myocardial infarction and stroke) and of end-organ injury of the blood vessels and tissue of the heart, brain, kidney, eye, and other organs.

5.6 **Michael H. Smolensky, Nicholas A. Peppas *et al.*,[4] 2007**, investigated on Chronobiology, drug-delivery and chronotherapeutics. chronotherapeutics is the delivery of medications in the right concentration to the right targeted tissues at the right time to meet biological rhythm-determined needs, Many chronic and acute medical conditions exhibit prominent circadian patterns of symptom manifestation and severity. Among the many examples are allergic rhinitis, bronchial asthma, and peptic ulcer disease; all tend to worsen overnight. The risk of many cardiovascular events, like angina pectoris, myocardial infarction, and thrombotic and hemorrhagic stroke, is greatest in the morning. The content of these articles clearly makes apparent many potential new applications of existing drug-delivery systems and devices, and it serves also as the basis for future developments.

5.7 **Sarasija Suresh**, **H.N. Shivakumar, *et al.*,[27] 2007**, studied on Design and evaluation of pH sensitive minitablets for chronotherapeutic delivery of Theophylline. The system comprising of Eudragit S-100 coated minitablets was designed for specifically target the nocturnal peak symptoms of asthma. The drug loaded core minitablets were produced by wet granulation method using alcoholic solution of PVP K30 as a binder. Different coat weights of Eudragit S-100 were applied to the drug loaded core minitablets to produce the pH sensitive minitablets. *In vitro* dissolution studies showed that a coat weight of 10% was sufficient for effective release of the drug at higher pH values.

5.8 **Sarasija Suresh**, **H.N. Shivakumar, *et al.,*[28] 2006**, studied on design and evaluation of controlled onset extended release multiparticulate systems for chronotherapeutic delivery of Ketoprofen. It consists of drug-loaded cellulose acetate cores encapsulated with in Eudragit S-100 microcapsules was designed for chronotherapeutic delivery of ketoprofen. Drug-loaded cellulose acetate cores were prepared by emulsion solvent evaporation technique in an oily phase at different drug: polymer ratios (1:1, 2:1 and 4:1).these cores were successfully microencapsulated with Eudragit S-100 following the same technique at the core:coat ratio of 1:5. SEM revealed that the cellulose acetate cores were discrete, uniform& spherical. The aim was to minimize drug release in the upper part of the GI tract and target the drug to the colon.

5.9 **Qureshi.J, Mohd**, **Sanjula Baboota, *et al.,*[29] 2006**, investigated on Pulsatile drug delivery system having a peculiar mechanism of delivering the drug rapidly & completely after a “lag time”. i.e., a period of “no drug release” though most delivery systems are designed for constant drug release over a prolonged period of time, constant blood levels of a drug may not always desirable. Pulsatile systems are designed in a manner that the drug is available at the site of action at the right time in the right amount.

5.10 **D. Searle. LLC, *et al.,*[30] 2006**, Covera-HS has a unique controlled-onset extended-release (COER) delivery system, which is designed for bedtime dosing, results in a maximum plasma concentration (C_{max}) of verapamil in the morning hours. Covera-HS was evaluated in two placebo-controlled, parallel design, double-blind studies of 382 patients with mild to moderate hypertension. In a clinical trial, 287 patients were randomized to placebo, 120 mg, 180 mg, 360 mg, or 540 mg and treated for 8 weeks (the two higher doses were titrated from low doses and maintained for 6 and 4 weeks, respectively). Covera-HS or placebo was given once daily at

10 pm and blood pressure changes were measured with 36-hour ambulatory blood pressure monitoring (ABPM). The results of these studies demonstrate that Covera-HS, at 180–540 mg, is a consistently and significantly more effective antihypertensive agent than placebo in reducing ambulatory blood pressures.

5.11 **Sarasija Suresh, H.N. Shivakumar, *et al.*,[31] 2006**, studied on pH sensitive multi-particulate systems for chronotherapeutic delivery of Diltiazem hydrochloride. The drug loaded core pellets were produced by aqueous extrusion spheronization technique using MCC as a spheronizing aid and PVP K30 as a binder. Different coat weights of several acrylic polymers were applied to the drug loaded pellets in an automatic coating machine. It was found that Eudragit S-100 shows a lag time of 5 hours at pH 7.0. The rapid drug release following an initial lag phase would ensure adequate protection in BP patients with early morning surge.

5.12 **Shan-Yang Lin and Mei-Janeli *et al.*,[33] 2004**, Formulation Design of Double-layer in the Outer Shell of Dry-coated Tablet to Modulate Lag Time and Time-controlled Dissolution Function: Studies on Micronized Ethyl cellulose for Dosage Form Design It consists of ethyl cellulose (EC) powder with a coarse particle (167.5μm) and several fine particles (<6 μm), respectively, were mixed toformulate the whole layer of the outer shell of dry-coated tablets. The formulations containing different weight ratios of coarse/fine particles of EC powders or 167.5 μm EC powder/excipient in the upper layer of the outer shell to influence the release behavior of sodium diclofenac from dry-coated tablet were also explored. The results indicate that sodium diclofenac released from all the dry-coated tablets exhibited an initial lag period, followed by a stage of rapid drug release. When the mixture of the coarse/fine particles of EC powders was incorporated into the whole layer.

5.13 **Yaw-Bin Huang**, **Yi-Hung Tsai, *et al.*,[34] 2004,** studied on formulation design and in vitro/in vivo investigation of Once-daily propranolol extended-release tablet dosage form, it is composed of three formulation variables: the content of HPMC (X1); MCC (X2); and lactose (X3): The drug release percent at 1.5, 4, 8, 14 and 24 h were the target responses and were restricted to 15–30, 35–55, 55–75, 75–90 and 90–110%, respectively. The results showed that the optimized formulation provided a dissolution pattern equivalent to the predicted curve, which indicated that the optimal formulation could be obtained using response surface methodology. The mechanism of drug release from HMPC matrix tablets followed non-Fickian diffusion. In the vivo study, the MRT was prolonged for matrix tablets when compared with commercial immediate release tablets.

5.14 **Mukai B., Utoguchi N *et al.*,[35] 2002**, prepared and evaluated the press-coated Aminophylline tablet using crystalline cellulose and PEG in the outer shell for timed-release dosage forms. The core tablet is prepared by direct compression method using rotary tablet punching machine. Press coating of core tablets using different ratios of crystalline cellulose and PEG. Tablets are evaluated for In-vitro dissolution test showed a lag time of 6 hours.

5.15 **Kung-Hsu Lin *et al.*,[36] 2001**, studied the influence of compression force to inner core tablet (or) to outer coating layer of the compression-coated tablet on the function of the time controlled release. Tabletting was performed under a compression force of 1190–1530 kg/cm^2 using a rotary tabletting machine (CLEANPRESS correct 12HUK kikusui Seisakusho, Kyoto, Japan). Concave punches 6 mm in diameter (curvature radius: 8 mm) were used for preparation of the core tablets. Compression of core tablets with different ratios of polymers content under a compression force of 990-1140 kg/cm^2. It was found that perfect

drug release was achieved with the compression force of 1120 kg/cm^2.

5.16 **Martti Marvola *et al.*,[37] 2001**, studied the development and biopharmaceutical evaluation of press-coated tablets with the intention of administering formulation in the evening at 22:00, which provides treatment for diseases in which symptoms are experienced in the early morning hours i.e**.** chronopharmacotherapy. The focus is to optimally deliver the drug in higher amounts in early morning hours (i.e. at time of greatest need) and lower amounts at night (i.e. when the need of drug is less).

5.17 **Michael H. Smolensky and Erhard Haus *et al.*,[1] 2001**, Circadian rhythms and clinical medicine with applications to hypertension. illustrating the human circadian time structure is to depict the peak time of 24-h rhythms on a clock-like diagram and circadian rhythm of diseases and chronotherapeutics. It is found that Evening verapamil chronotherapy (Verelan PM and Covera-HS) achieves more complete 24-h BP control than once-a-day conventional constant-release medications.

5.18 **Madhusudan, Hariharan *et al.*,[38] 2001**, developed a novel compression coated tablet dosage form which describes the dosage form not requires the separate formation of the core tablet because the core material and outer compression coating material are formed into a tablet in the same tablet press and on a single turret.

5.19 **Michael Prisant .L *et al.*[3] 2001**, reported on Biologic rhythms are implicated in cardiovascular events. Failure to recognize the circadian decline in blood pressure may result in iatrogenic chronopathological events, including anterior ischemic optic neuropathy and cerebrovascular accidents. Novel drug delivery

systems have the potential to provide antihypertensive medication at the time when the need is greatest. For the treatment of hypertension, this idea has the potential for a therapeutic paradigm shift Chronotherapeutics is the purposeful alteration of drug level to match rhythms to optimize therapeutic outcomes and minimize size effects for the treatment of hypertension.

5.20 **Eiji Fukui*, Katsuji Uemura, *et al.*,[39] 2000**, Studied on applicability of press-coated tablets using hydroxypropylcellulose (HPC) in the outer shell for timed-release preparations. It contains diltiazem hydrochloride (DIL) in the core tablet and coated with hydroxypropylcellulose (HPC) as the outer shell, were examined for applicability as timed-release tablets with a predetermined lag time and subsequent rapid drug release phase. Two different kinds of timed-release press-coated tablets that showed lag times of 3 and 6 h in the *in vitro* test (denoted PCT_{L3} and PCT_{L6} respectively) were administered to beagle dogs. The lag times showed a good agreement between the *in vivo* and *in vitro* tests in PCT_{L3}. However, the *in vivo* lag times were about 4 h in PCT_{L6} and were much shorter than the *in vitro* lag time.

5.21 ***White WB, Fakouhi T et al.,[40] 1998****, studied Comparison of effects of controlled onset extended release verapamil at bedtime and nifedipine (GITS).* ***The study was a multicenter (n = 51), randomized, double-blind prospective clinical trial with a 10-week treatment period. Ambulatory BP monitoring was performed at placebo baseline, after 4 weeks of stable double-blind therapy, and at end of the study. Twenty-four-hour BP profiles were studied in 557 hypertensive patients. Changes in BP, HR, slope of the rate of rise of BP and HR, and the HR-systolic BP product during the 4 hours from 1 hour before to 3 hours after awakening were evaluated. It was found that***

COER-verapamil and nifedipine GITS had equivalent effects (+/- 5/3 mm Hg) on early morning BP.

5.22 **Richard J. Martin,MD**, **Monica Kraft, *et al.,*[32] 1995**, investigated in Chronobiology and Chronotherapy in Respiratory medicine. It was found that, Chronotherapeutic delivery of theophylline, once daily in the evening between 6 p.m & 7 p.m controls Asthma nocturnal symptoms and early morning bronchoconstriction. This regimen has been found to be clinically superior to conventional twice-daily dosing.

6. MATERIALS AND EQUIPMENTS

Table 7: Materials used

Material	Grade	Source
Propranolol Hcl	IP	Tristar formulation
Hydroxy propyl methyl cellulose	K15M	Sigma-aldrich
Microcrystaline cellulose	DC	Himedia Laboratories
Ethyl Cellulose	22 cp	S.D fine chemicals
Xanthan gum	-	Himedia Laboratories
Guar gum	M.W: 2,20,000	Himedia Laboratories
Magnesium stearate	-	S.D fine chemicals
Talc	-	S.D fine chemicals

Table 8 : Equipments used

Equipment	Model / Company
Tablet punching machine	Rimek Mini press
UV-visible spectrophotometer	Jasco V-530
FT-IR spectrophotometer	Jasco 410
Digital balance	Denver instruments
Dissolution test apparatus	Lab India disso 2000
Hardness tester	Pfizer
Friabilator	Camp-bell, India
Hot air oven	Inlab equipments
Electronic vernier caliper	Mitutoyo (India)
pH meter	Metrohm, Switzerland

7. PRE-FORMULATION STUDIES

Before formulation of drug substances into a dosage form, it is essential that it should be chemically and physically characterized. Preformulation studies give the information needed to define the nature of the drug substance and provide a framework for the drug combination with pharmaceutical excipients in the fabrication of a dosage form.

In the present work, preformulation studies on the purity, development of calibration curve of the drug candidate and the compatibility between drug and excipients were carried out.

7.1 DEVELOPMENT OF CALIBRATION CURVE FOR PROPRANOLOL HYDROCHLORIDE

Spectral measurement

The standard solution of Propranolol Hcl was scanned between 400 and 200 nm using UV-visible spectrophotometer.

7.1.1 Procedure for standard graph

A spectrophotometric method based on the measurement of absorbance at 290nm[17] in phosphate buffer of pH 6.8 was used in the present study for the estimation of Propranolol hydrochloride (Indian pharmacoepia, 1996).

An accurately weighed 100 mg of Propranolol Hydrochloride was dissolved in phosphate buffer of pH 6.8 in a 100 ml volumetric flask and the solution was made up to the volume with phosphate buffer of pH 6.8 to give 1 mg/ml solution. From the above solution 10 ml was diluted to 100 ml using phosphate buffer to give 100µg/ml working stock solution. The above working stock solution was subsequently diluted with phosphate

buffer of pH 6.8 to obtain a series of dilutions containing 10, 20, 30, 40 and 50 µg/ml of solution. The λ_{max} of the drug was determined by scanning the dilutions between 400 and 200 nm using a Shimadzu 1400 double beam UV-visible spectrophotometer. At this wavelength, the absorbances of all the other solutions are measured using the phosphate buffer of pH 6.8 as blank. The concentrations of Propranolol hydrochloride and the corresponding absorbance values are given in table. The absorbance values were plotted against concentrations of Propranolol hydrochloride as shown in fig 5. The method obeys Beer-Lambert's law in the concentration range of 10-50 µg/ml.

7.1.2 Preparation of pH 6.8 phosphate buffer [16]

Place 50 ml of the 0.2 M potassium dihydrogen phosphate solution in a 200 ml standard volumetric flask and add 22.4 ml of 0.2M sodium hydroxide solution to this flask and make up the volume with distilled water.

- **Potassium dihydrogen phosphate, 0.2 M solution**

Take accurately weighed 27.22 gm of Potassium dihydrogen phosphate and dissolved in 1000 ml of distilled water, this will give 0.2 M KH_2PO_4.

- **Sodium hydroxide 0.2 M solution**

Take accurately weighed 8 gm of sodium hydroxide and dissolved in 1000 ml of distilled water, this will give 0.2 M NaOH solution.

Table 9: Standard graph of Propranolol hydrochloride in phosphate buffer pH 6.8

Sl. No.	Concentration (µg/ml)	Absorbance at 290 nm
1	0	0.000
2	10	0.210
3	20	0.426
4	30	0.642
5	40	0.851
6	50	1.097

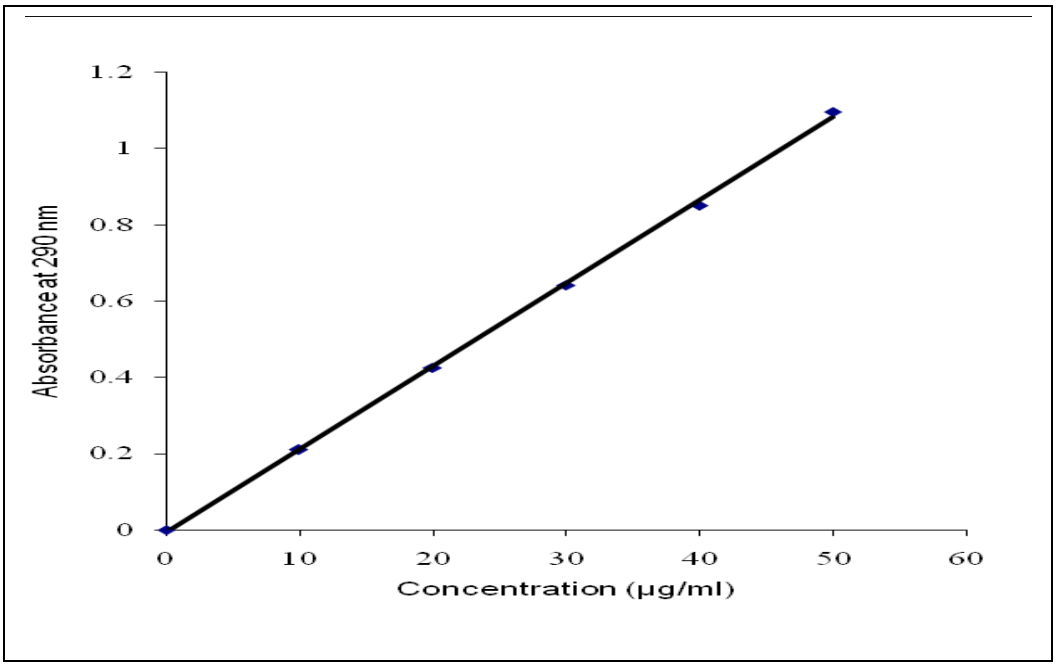


Fig 5: Standard graph of Propranolol hydrochloride in phosphate buffer pH 6.8

7.2 COMPATIBILITY STUDIES

One of the requirements for the selection of suitable excipients or carrier for pharmaceutical formulation is its compatibility. Therefore in the present work, a study was carried out by using infrared spectrophotometer to find out if there is any possible interaction between the drug and excipients.

Weighed amount of drug (3mg) was mixed with 100 mg of potassium bromide (dried at 40-50°C). The mixture was taken and compressed under 10-ton pressure in a hydraulic press to form a transparent pellet. The pellet was scanned from 4000-400 cm^{-1} in IR spectrophotometer.

7.2.1 IR Spectral Analysis

Using FTIR spectrometer the compatibility studies between drugs and the carriers was carried out. There was no appearance or disappearance of any characteristic peak, which confirms the absence of chemical interaction between drug and carrier.

Principal peaks at wave numbers 1103, 1270, 772, 1580, 795, 1240 (Propranolol hydrochloride, KBr disc).

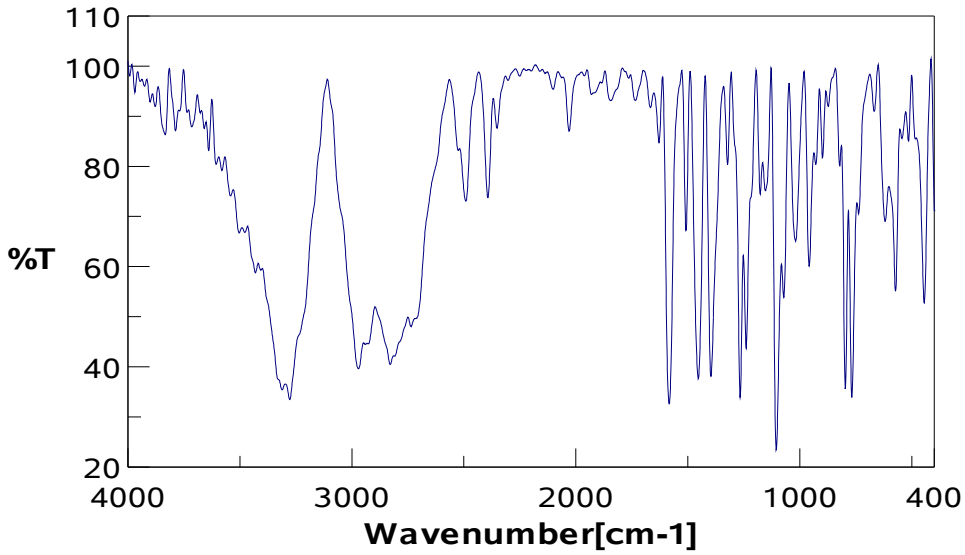


Fig 6: IR spectrum of propranolol Hcl

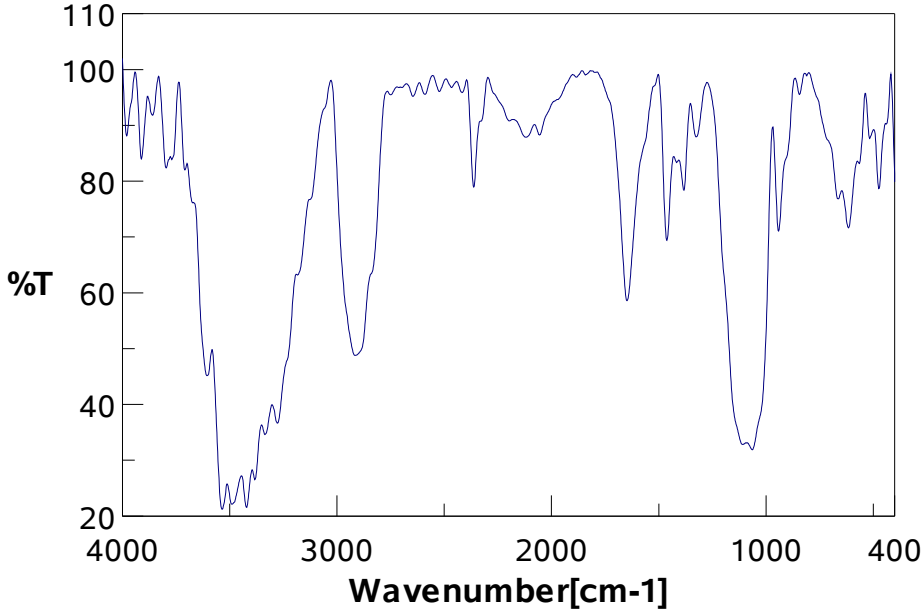


Fig 7: IR spectrum of HPMC polymer

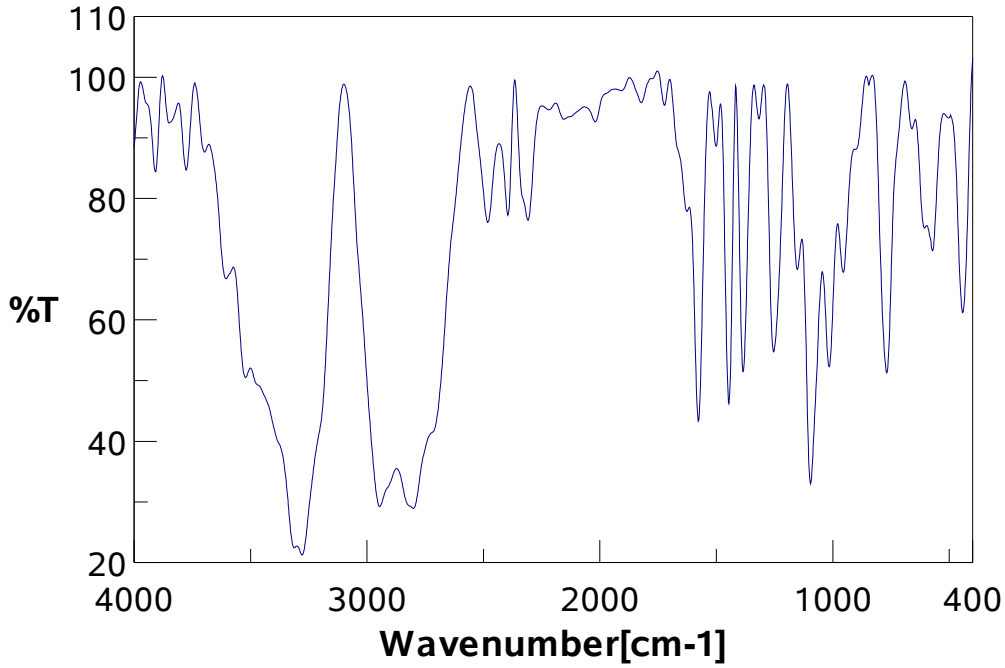


Fig 8: IR spectrum of core tablet (Drug + HPMC)

8. FORMULATION OF CONTROLLED ONSET EXTENDED RELEASE TABLETS

The different formulations of propranolol hydrochloride controlled onset extended release tablets were formulated by press-coating technique under direct compression method using a combination of hydrophobic polymer ethylcellulose and natural swellable polymers xanthan gum and guar gum as outer coating layer.

8.1 FORMULATION OF CORE TABLETS

The core tablets containing drug, HPMC and MCC, were prepared by weighing all the ingredients and passed through sieve no.80 and mixed in a geometrical dilution method. Magnesium stearate and talc (1% each) were added to each blend and further mixed. The resultant blends were tableted to 200 mg using concave punches in a rotary tabletting machine (Rimek minipress, India).

8.2 PRESS-COATING OF CORE TABLETS

The composition of the tablets is given in Table 10. Ethyl cellulose (EC) and each mixture of xanthan gum and guar gum were passed through a sieve no.80 and 150 mg of the powder mixture was used for the outer shell. Different weight ratios of (w/w) of EC/excipient mixture were formulated as shown in Table 10. The press-coating of tablets was performed using a rotary tabletting machine (Rimek minipress, India). A half amount of the EC/excipient mixture was filled into the die to make a powder bed, on the centre of which was placed the core tablet. Then, the remaining half of the EC/excipient mixture was filled in the die and the contents were compressed to prepare the compression-coated tablet.

Table 10: The composition and formulation code for various COER tablets containing propranolol Hcl

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S. No.	Ingredients mg/tab	Formulation code								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1.	Propranolol Hcl	100	100	100	100	100	100	80	120	100
2.	HPMC	30	30	30	30	30	30	30	30	50
3.	Microcrystalline cellulose	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
4.	Ethyl cellulose	75	100	50	75	100	50	75	75	75
5.	Xanthan gum	75	50	100	-	-	-	75	75	75
6.	Guar gum	-	-	-	75	50	100	-	-	-
7.	Magnesium stearate	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
8.	Talc	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

Table 11: The composition and formulation code of various PCT containing propranolol Hcl using EC & xanthan gum as outer coat.

S. NO.	Formulation Code	EC	Xanthan Gum	IN RATIOS
1	F1	75mg	75 mg	(1:1)
2	F2	100 mg	50 mg	(2:1)
3	F3	50 mg	100 mg	(1:2)
4	F7	75 mg	75 mg	(1:1)
5	F8	75 mg	75 mg	(1:1)
6	F9	75 mg	75 mg	(1:1)

Table 12: The composition and formulation code of various PCT containing propranolol Hcl using EC & guar gum as outer coat.

S. NO	Formulation Code	EC	Guar gum	IN RATIOS
1	F4	75mg	75 mg	(1:1)
2	F5	100 mg	50 mg	(2:1)
3	F6	50 mg	100 mg	(1:2)

The hydrophilic gums are extensively used for oral extended release dosage forms due to their simplicity, cost effectiveness and reduction of the risk of systemic toxicity due to dose dumping. Furthermore, pH-independent drug release is preferable for oral extended release formulations, so as not to be affected by intra- and inter-subject variations of both gastric pH and GI transit time. The hydroxypropylmethylcellulose (HPMC) is a pH-independent material and the drug release rates from HPMC matrix formulations are generally independent of processing variables such as compaction pressure, drug particle size, and the incorporation of a lubricant .Therefore, HPMC is widely used to prepare extended release dosage forms.

9. EVALUATION OF TABLETS

The formulated tablets were subjected for the following quality control tests:

- Weight variation
- Hardness
- Friability
- Thickness
- Drug content uniformity
- Compatibility studies
- *In vitro* dissolution studies

9.1 WEIGHT VARIATION TEST

Ten tablets were weighed individually as per USP. They were evaluated for the weight variations. The weight variation allowed as per USP limit is 5%. The weights of tablet were within the USP limits. The results are shown in Table no 14 & 15.

Table 13: Standard data of percentage deviation of tablets as per USP

Pharmaceutical form	Average mass	% Deviation
Tablets	≤130 mg	± 10
	> 130 mg - 324 mg	± 7.5
	≥ 325 mg	± 5

Table 14: Weight variation of various PCT containing propranolol Hcl using EC/Xanthan gum as an outer coat

S. No.	Formulation code	Weight range of 10 tablets in mg	Average weight in mg	Limit range (± 5%)
1	F1	345 – 358	351	333.5 - 368.5
2	F2	342 – 357	351	333.5 - 368.5
3	F3	346 – 357	350.5	332.9 - 368.1
4	F7	340 – 358	350.4	332.9 - 367.9
5	F8	345 - 360	351	333.5 - 368.5
6	F9	342 – 358	350.2	332.7 - 367.7

Table 15: Weight variation of various PCT containing propranolol Hcl using EC/ Guar gum as an outer coat

S. No.	Formulation code	Weight range of 10 Tablets in mg	Average weight in mg	Limit range (± 5%)
1	F4	345 – 356	350.4	332.9 - 367.9
2	F5	338 – 356	349.5	332.1 - 366.9
3	F6	342 – 357	350	332.5 - 367.5

9.2 FRIABILITY TEST

Friability test was performed on the formulated tablets using Roche friabilator (Camp-bell electronics, India), The weight of the tablets after undergoing 100 revolutions was found to be within the limits 0.5 to 1.0%. The results are shown in Table 16 &17.

9.3 HARDNESS

Pfizer hardness tester was used for measuring the hardness of formulated propranolol TCR tablets. Five tablets were taken randomly and subjected to test. The hardness was found to be 4-6 kg/cm^2. The results are shown in Table 16 & 17.

9.4 THICKNESS

Uniform compression force and volume of die fill leads to uniform thickness. From each batch, 3 tablets were taken and checked with a electronic thick-ness gauge (Mitutoyo, India) and the results are shown in Table 16.

Table 16: Hardness, friability, thickness of various PCT containing propranolol Hcl using EC/Xanthan gum as an outer coat.

S. No.	Formulation code	Hardness (kg/cm^2)	Friability (%)	Average thickness in mm
1	F1	5.1	0.14	2.44
2	F2	5.2	0.19	2.61
3	F3	5.4	0.06	2.64
4	F7	5.0	0.14	3.16
5	F8	4.9	0.56	2.55
6	F9	5.7	0.06	2.71

Table 17: Hardness, friability, thickness of various PCT containing propranolol Hcl using EC/Guar gum as an outer coat.

S. No.	Formulation code	Hardness (kg/cm^2)	Friability (%)	Average thickness in mm
1	F4	5.6	0.03	3.04
2	F5	5.3	0.11	2.92
3	F6	5.4	0.09	2.75

9.5 DRUG CONTENT UNIFORMITY[16]

The prepared tablets containing propranolol Hcl was tested for drug content uniformity. Transfer one tablet to a 100 ml volumetric flask which was previously clean and dry. 5 ml of dilute Hcl (1 in 100) was added and swirled occasionally until it is disintegrated, about 70 ml of methanol was added and sonicated for about one minute. Diluted with methanol to volume, mix and centrifuge a portion of the solution and measured the

absorbance of resulting solution at 290 nm in a Jasco V530 UV visible spectrophotometer. The results are shown in Table 18 & 19.

Table 18: Drug content uniformity for various PCT containing propranolol Hcl using EC/xanthan gum as an outer coat

S. No.	Formulation code	Amount of propranolol per tablet	
		Amount in milligram	% purity
1	F1	99.51	99.5 %
2	F2	99.25	99.3 %
3	F3	100.25	100.3 %
4	F7	79.60	99.5 %
5	F8	117.6	99.8 %
6	F9	100.75	100.8 %

Table 19: Drug content uniformity for various PCT containing propranolol Hcl using EC/guar gum as an outer coat

S. No.	Formulation code	Amount of propranolol per Tablet	
		Amount in milligram	% purity
1	F4	101.0	101 %
2	F5	99.2	99.2 %
3	F6	99.0	99%

9.6 IN VITRO DISSOLUTION STUDIES[34]

In vitro release of propranolol Hcl from nine different formulations were carried out by using dissolution paddle assembly (Lab india Disso 2000) containing 900 ml of hydrochloric acid buffer (pH 1.2) for 2 hrs and 900 ml of phosphate buffer (pH 6.8) for 22 hrs at 100 rpm and 37± 0.5°C. The 5 ml of samples were collected from each formulation in time interval of 1 hour till 8 hours and 12, 16, 20 and 24th hours. Diluted suitably and

analysed at 290 nm in UV spectrophotometer, from the results the cumulative percentage drug release of propranolol Hcl from each press-coated tablets were estimated using an equation obtained from standard curve (fig.5). The percentage release of propranolol Hcl from press-coated tablets are shown in the following Table 20.

Table 20: Percentage *Invitro* release of various COER tablets containing propranolol Hcl using various buffers.

Time (hrs)	Percentage release of propranolol Hcl from PCT								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	0	0	0	0.2	0	1.5	0	0	0
2	0	0	0	2.3	0	5.3	0	0	0
3	0	0	2.3	7.4	0	8.2	0	0	0
4	4.2	0	6.1	11.5	0	18.4	3.6	4.5	3.3
5	11.6	0	12.6	23.7	0	29.5	9.8	8.2	6.4
6	21.2	12.5	24.5	36	14.5	42.4	21.2	24.1	19.5
7	34.6	23.6	36.2	55.6	29.4	49.2	30.8	32.6	26.9
8	43.8	38.5	46.5	74.3	39.6	68.6	40.2	42.7	34.8
12	70.4	68.1	72.9	82.3	69.5	86.1	71.2	73.4	62.1

16	85.8	80.2	86.9	95.1	81.3	99.5	82.8	83.5	74.5
20	96.3	91.4	99.2	99.3	93.8	-	92.3	91.7	86.2
24	99.9	99.9	-	-	99.4	-	99.8	99.6	92.7

Table 21: Dissolution profile of the chronotherapeutic formulation F1* containing propranolol Hcl using buffer pH 1.2 and 6.8

Time (hr)	Absorbance (290 nm)	Amount (µg/ml)	Amount (mg/900ml)	Cumulative %release
1	0.000	0	0	0
2	0.000	0	0	0
3	0.000	0	0	0
4	0.0552	4.670	4.203	4.2
5	0.1510	12.84	11.556	11.6
6	0.2784	23.5	21.198	21.2
7	0.4544	38.44	34.600	34.6
8	0.5752	48.67	43.799	43.8
12	0.9245	78.22	70.396	70.4
16	1.1267	95.33	85.793	85.8
20	1.2646	107.0	96.300	96.3
24	1.3119	111.0	99.895	99.9

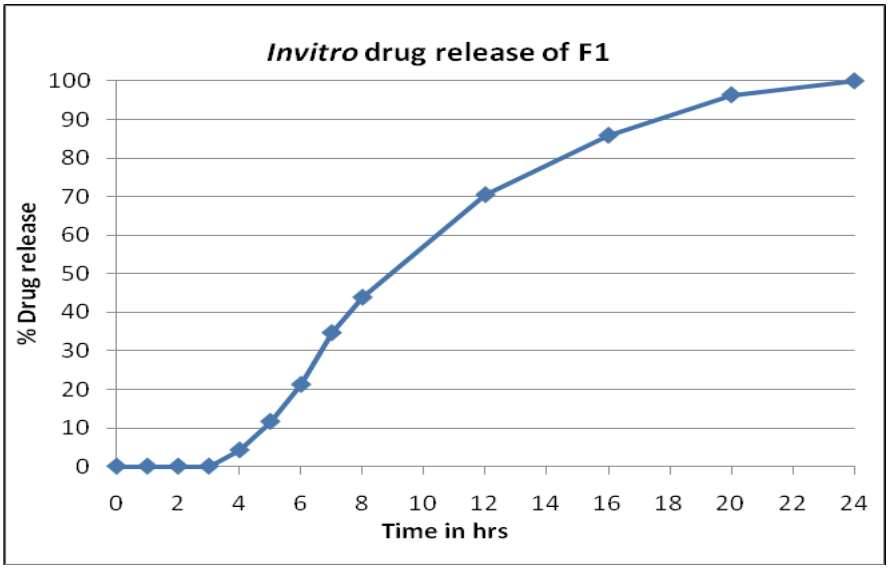

Fig 9: Percentage drug release of propranolol Hcl from COER tablets containing EC/Xanthan gum (1:1) as an outer coat using buffer pH 1.2 and 6.8

Table 22: Dissolution profile of the chronotherapeutic formulation F2* containing propranolol Hcl using buffer pH 1.2 and 6.8

Time (hr)	Absorbance (290 nm)	Amount (µg/ml)	Amount (mg/ 900ml)	Cumulative %release
1	0.000	0	0	0
2	0.000	0	0	0
3	0.000	0	0	0
4	0.000	0	0	0
5	0.000	0	0	0
6	0.1642	13.88	12.503	12.5
7	0.3099	26.22	23.599	23.6
8	0.5056	42.77	38.501	38.5
12	0.8944	75.67	68.107	68.1
16	1.0532	89.11	80.200	80.2
20	1.2003	101.56	91.403	91.4
24	1.3119	111.00	99.895	99.9

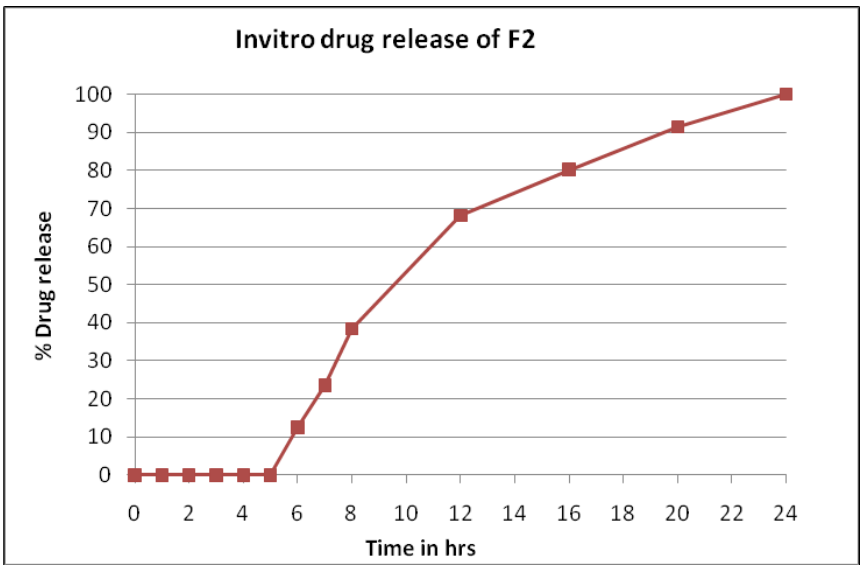

Fig 10: Percentage drug release of propranolol Hcl from COER tablets containing EC/Xanthan gum (2:1) as an outer coat using buffer pH 1.2 and 6.8

Table 23: Dissolution profile of the chronotherapeutic formulation F3* containing propranolol Hcl using buffer pH 1.2 and 6.8

Time (hr)	Absorbance (290 nm)	Amount (µg/ml)	Amount (mg/900ml)	Cumulative %release
1	0.000	0	0	0
2	0.000	0	0	0
3	0.0302	2.56	2.301	2.3
4	0.0801	6.78	6.102	6.1
5	0.1655	14.00	12.600	12.6
6	0.3217	27.22	24.501	24.5
7	0.4754	40.22	36.201	36.2
8	0.6106	51.67	46.502	46.5
12	0.9573	81.00	72.903	72.9
16	1.1412	96.55	86.903	86.9
20	1.3027	110.22	99.204	99.2
24	-	-	-	-

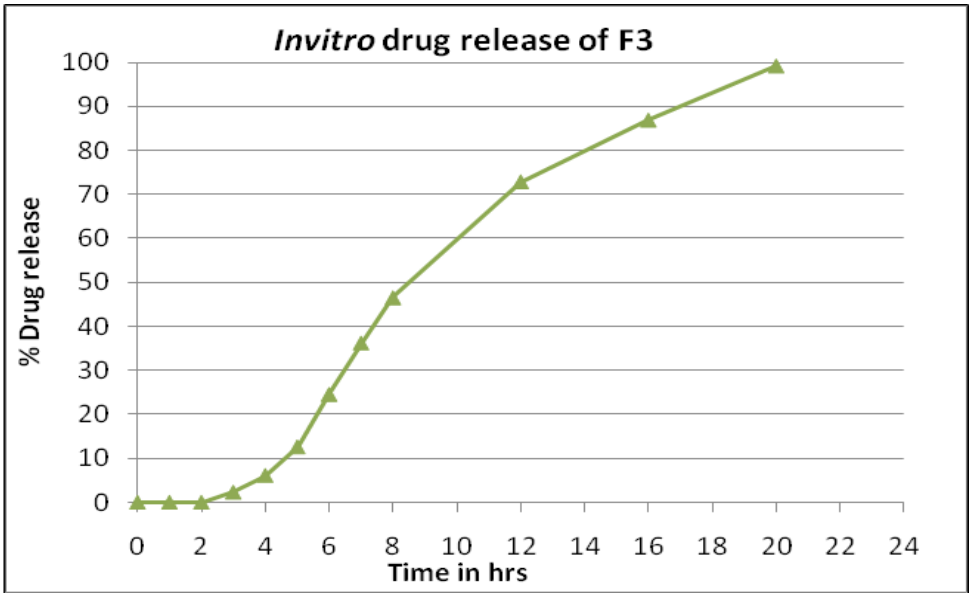

Fig 11: Percentage drug release of propranolol Hcl from COER tablets containing EC/Xanthan gum (1:2) as an outer coat using buffer pH 1.2 and 6.8

Table 24: Dissolution profile of the chronotherapeutic formulation F4* containing propranolol Hcl using buffer pH 1.2 and 6.8

Time (hr)	Absorbance (290 nm)	Amount (µg/ml)	Amount (mg/900ml)	Cumulative %release
1	0.0026	0.222	0.199	0.2
2	0.0302	2.56	2.300	2.3
3	0.0972	8.22	7.400	7.4
4	0.1510	12.78	11.501	11.5
5	0.3112	26.33	23.70	23.7
6	0.4727	40.0	36.001	36.0
7	0.7301	61.77	55.595	55.6
8	0.9757	82.55	74.303	74.3
12	1.0808	91.44	82.303	82.3
16	1.2489	105.66	95.104	95.1
20	1.3041	110.33	99.304	99.3
24	-	-	-	-

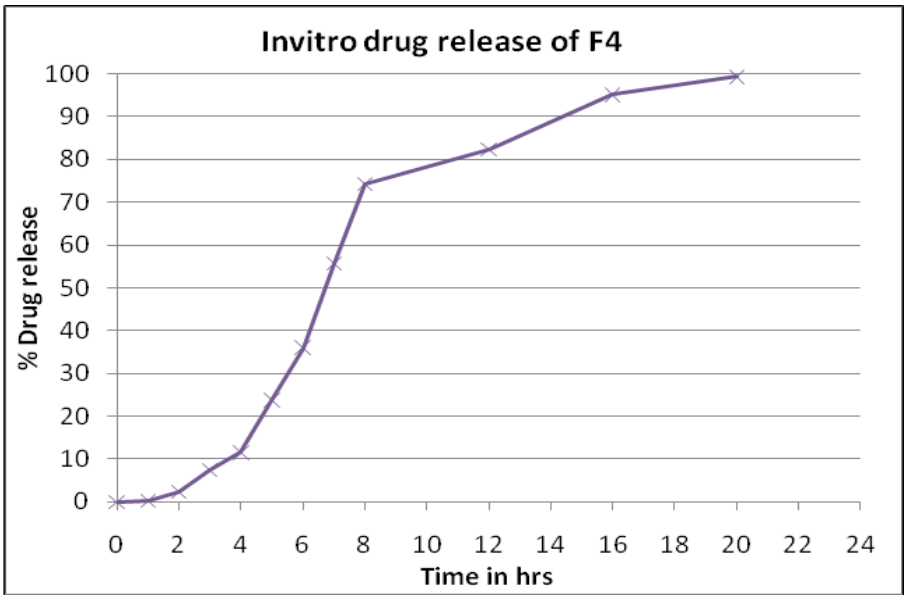

Fig 12: Percentage drug release of propranolol Hcl from COER tablets containing EC/guar gum (1:1) as an outer coat using buffer pH 1.2 and 6.8

Table 25: Dissolution profile of the chronotherapeutic formulation F5* containing propranolol Hcl using buffer pH 1.2 and 6.8

Time (hr)	Absorbance (290 nm)	Amount (µg/ml)	Amount (mg/900ml)	Cumulative %release
1	0.000	0	0	0
2	0.000	0	0	0
3	0.000	0	0	0
4	0.000	0	0	0
5	0.000	0	0	0
6	0.1904	16.11	14.5	14.5
7	0.3861	32.66	29.401	29.4
8	0.5201	44.0	39.601	39.6
12	0.9127	77.22	69.502	69.5
16	1.0676	90.33	81.303	81.3
20	1.2318	104.22	93.804	93.8
24	1.3054	110.44	99.404	99.4

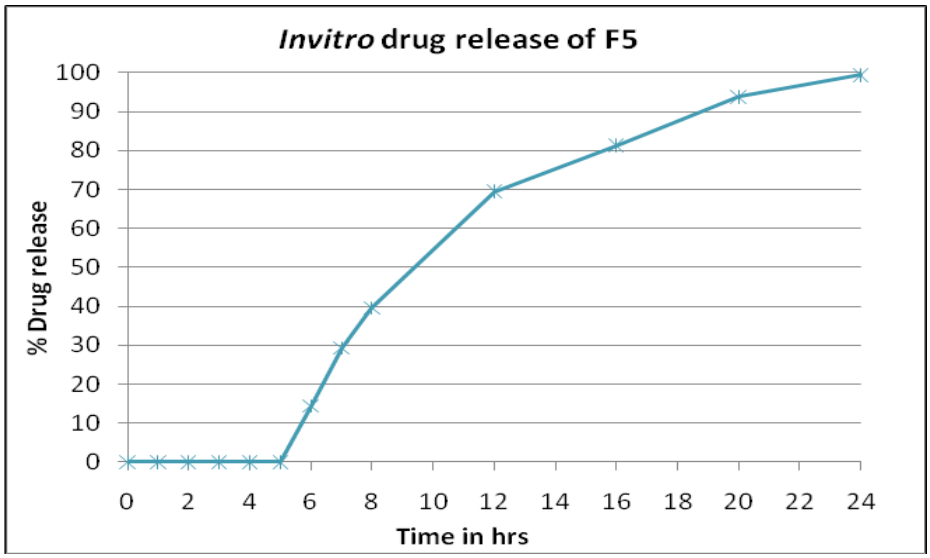

Fig 13: Percentage drug release of propranolol Hcl from COER tablets containing EC/guar gum (2:1) as an outer coat using buffer pH 1.2 and 6.8

Table 26: Dissolution profile of the chronotherapeutic formulation F6* containing propranolol Hcl using buffer pH 1.2 and 6.8

Time (hr)	Absorbance (290 nm)	Amount (µg/ml)	Amount (mg/900ml)	Cumulative %release
1	0.0196	1.667	1.500	1.5
2	0.0696	5.88	5.299	5.3
3	0.1077	9.11	8.20	8.2
4	0.2416	20.44	18.40	18.4
5	0.3874	32.77	29.50	29.5
6	0.5568	47.11	42.401	42.4
7	0.6461	54.66	49.202	49.2
8	0.9009	76.22	68.602	68.6
12	1.1307	95.66	86.103	86.1
16	1.3067	110.55	99.504	99.5
20	-	-	-	-
24	-	-	-	-

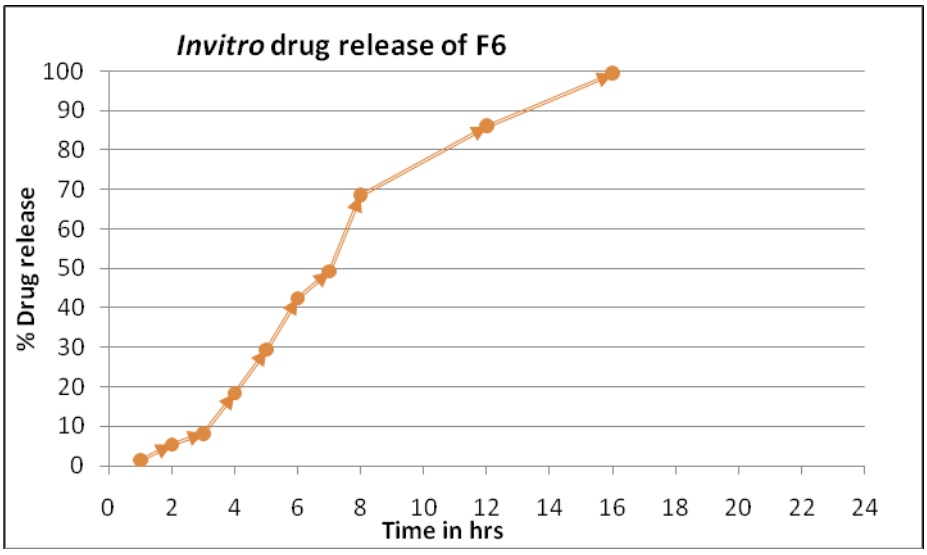

Fig 14: Percentage drug release of propranolol Hcl from COER tablets containing EC/guar gum (1:2) as an outer coat using buffer pH 1.2 and 6.8

Table 27: Dissolution profile of the chronotherapeutic formulation F7* containing propranolol Hcl using buffer pH 1.2 and 6.8

Time (hr)	Absorbance (290 nm)	Amount (µg/ml)	Amount (mg/900ml)	Cumulative %release
1	0.000	0	0	0
2	0.000	0	0	0
3	0.000	0	0	0
4	0.0378	3.20	2.880	3.6
5	0.1029	8.71	7.840	9.8
6	0.2227	18.84	16.960	21.2
7	0.3235	27.37	24.641	30.8
8	0.4223	35.73	32.161	40.2
12	0.7480	63.2	56.962	71.2
16	0.8699	73.6	66.242	82.8
20	0.9697	82.04	73.843	92.3
24	1.0485	88.71	79.843	99.8

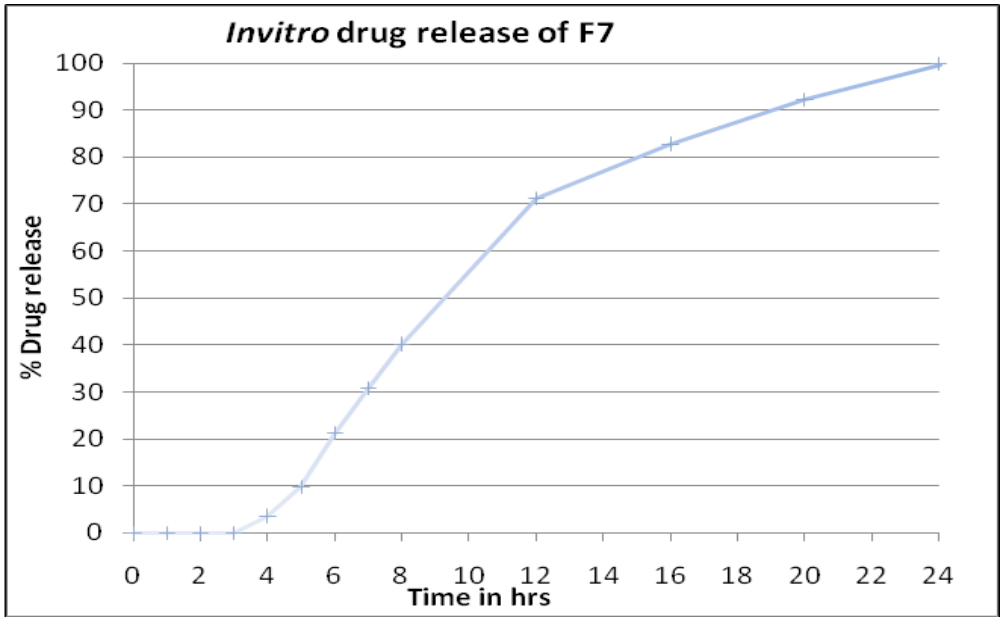

Fig 15: Percentage drug release of propranolol Hcl from COER tablets containing 80mg of drug and EC/Xanthan gum (1:1) as an outer coat using buffer pH 1.2 and 6.8

Table 28: Dissolution profile of the chronotherapeutic formulation F8* containing propranolol Hcl using buffer pH 1.2 and 6.8

Time (hr)	Absorbance (290 nm)	Amount (µg/ml)	Amount (mg/900ml)	Cumulative %release
1	0.000	0	0	0
2	0.000	0	0	0
3	0.000	0	0	0
4	0.0709	6.00	5.400	4.5
5	0.1292	10.93	9.840	8.2
6	0.3797	32.13	28.921	24.1
7	0.5137	43.46	39.121	32.6
8	0.6729	56.93	51.242	42.7
12	1.1567	97.86	88.083	73.4
16	1.3158	111.3	100.204	83.5
20	1.4451	122.3	110.044	91.7
24	1.5696	132.8	119.525	99.6

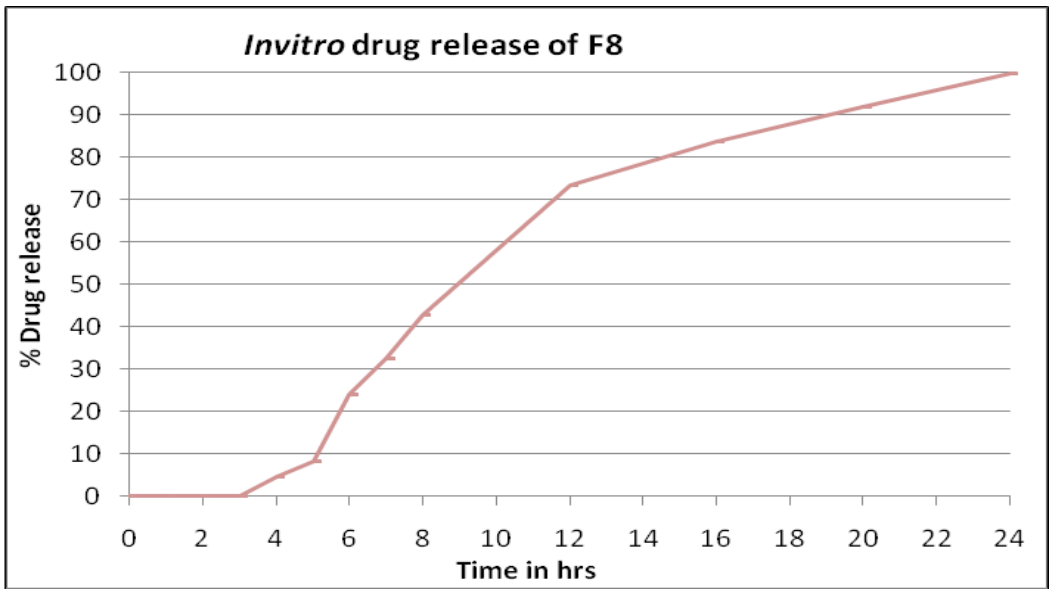

Fig 16: Percentage drug release of propranolol Hcl from COER tablets containing 120mg of drug and EC/Xanthan gum (1:1) as an outer coat using buffer pH 1.2 and 6.8

Table 29: Dissolution profile of the chronotherapeutic formulation F9* containing propranolol Hcl using buffer pH 1.2 and 6.8

Time (hr)	Absorbance (290 nm)	Amount (µg/ml)	Amount (mg/900ml)	Cumulative %release
1	0.000	0	0	0
2	0.000	0	0	0
3	0.000	0	0	0
4	0.0433	3.66	3.300	3.3
5	0.0841	7.11	6.400	6.4
6	0.2561	21.66	19.501	19.5
7	0.3532	29.88	26.901	26.9
8	0.457	38.66	34.801	34.8
12	0.8155	69.0	62.102	62.1
16	0.9783	82.77	74.503	74.5
20	1.1321	95.77	86.203	86.2
24	1.2174	103.0	92.704	92.7

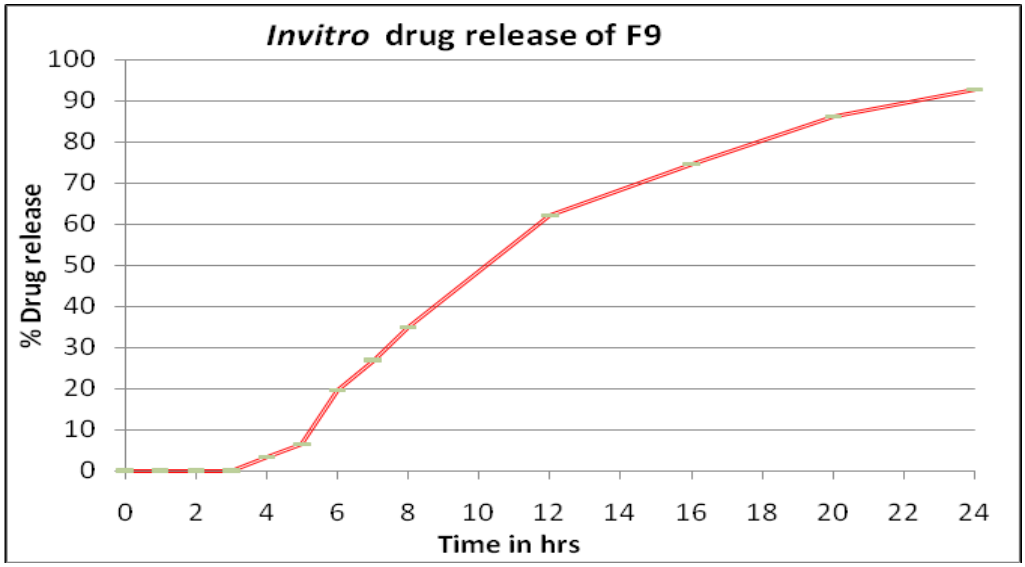

Fig 17: Percentage drug release of propranolol Hcl from COER tablets containing 50mg of HPMC in core tablets and EC/Xanthan gum (1:1) as an outer coat using buffer pH 1.2 and 6.8

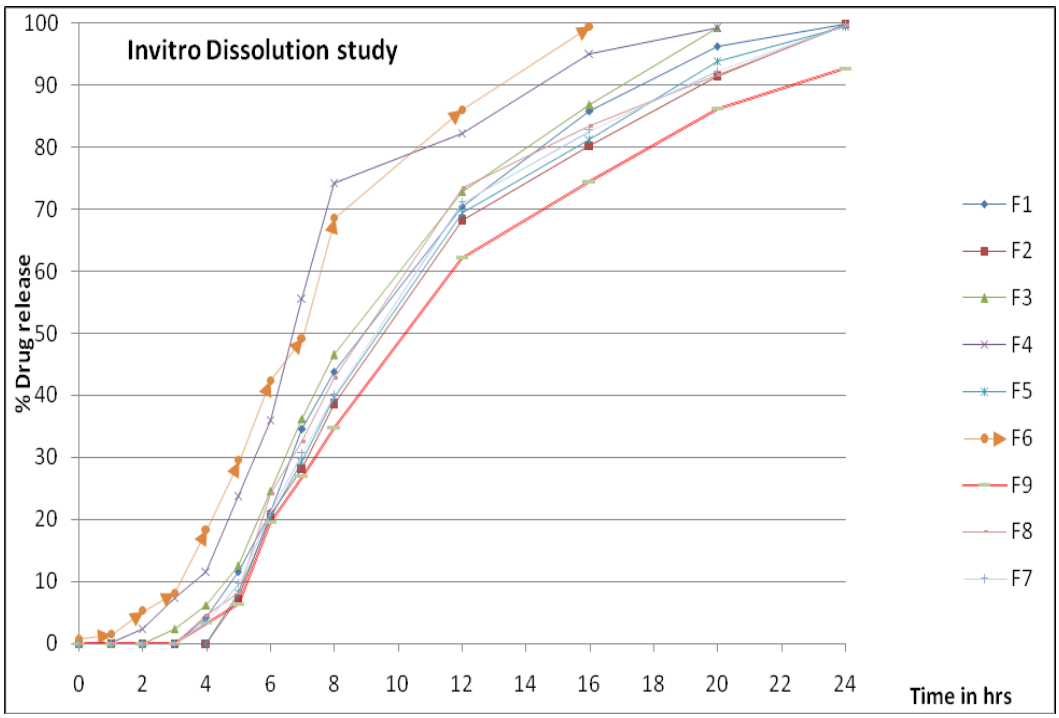

Fig 18: The comparative dissolution profile of various formulations [F1 – F9] in pH 1.2 and 6.8 for 24 hrs.

10. DRUG RELEASE KINETICS

Three categories of dissolution test specifications for drug products are described in the guidance. Single point specifications are recommended as a routine quality control test for highly soluble and rapidly dissolving drug products. This comparison method can be employed in evaluating scale-up and post-approval changes such as manufacturing site changes, component and composition changes, equipment changes and process changes. Two-point specifications are suggested for characterizing the quality of drug product and for accepting product sameness under SUPAC-related changes. In the presence of certain minor changes the single point dissolution test may be adequate to ensure unchanged product quality and performance. For more major changes a dissolution profile comparison performed under identical conditions for the product before and after the changes is recommended. Dissolution profiles may be considered similar by virtue of overall profile similarity and similarity at every dissolution sample time point.

Method used to compare dissolution data is:

- Model Dependent Methods (zero order, first order, Higuchi's, Korsmeyer's)

Drug Release Kinetics[41]

To study the release kinetics, data obtained from *in vitro* drug release studies were plotted in various kinetic models: zero order (Equation 1) as cumulative amount of drug released vs. time, first order

(Equation 2) as log cumulative percentage of drug remaining vs. time, and Higuchi's model (Equation 3) as cumulative percentage of drug released vs. square root of time.

$$C = K_0 t \qquad \text{(Equation 1)}$$

where K_0 is the zero-order rate constant expressed in units of concentration/time and t is the time in hours.

A graph of concentration vs. time would yield a straight line with a slope equal to K_0 and intercept the origin of the axes.

$$\log_c = \log C_0 - kt/2.303 \qquad \text{(Equation 2)}$$

where C_0 is the initial concentration of drug,

k is the first order constant, and t is the time.

$$Q = Kt^{1/2} \qquad \text{(Equation 3)}$$

where K is the constant reflecting the design variables of the system

t is the time in hours.

Hence, drug release rate is proportional to the reciprocal of the square root of time.

Drug release were plotted in Korsmeyer et al., equation (Equation 4) as log cumulative percentage of drug released vs. log time, and the exponent n was calculated through the slope of the straight line.

$$M_t / M_\infty = Kt^n \qquad \text{(Equation 4)}$$

where M_t/M_∞ is the fractional solute release, t is the release time,

K is a kinetic constant

Table 30: Drug release kinetics for various COER tablets containing propranolol HCl

Formulation	Zero Order R^2	First Order R^2	Higuchi's Plot R^2	Korsmeyer's Plot R^2
F1	0.944	0.847	0.951	0.970
F2	0.938	0.948	0.923	0.983
F3	0.960	0.949	0.947	0.979
F4	0.889	0.944	0.923	0.945
F5	0.934	0.891	0.925	0.984
F6	0.966	0.817	0.962	0.966
F7	0.947	0.828	0.949	0.969
F8	0.938	0.866	0.946	0.956
F9	0.956	0.935	0.950	0.961

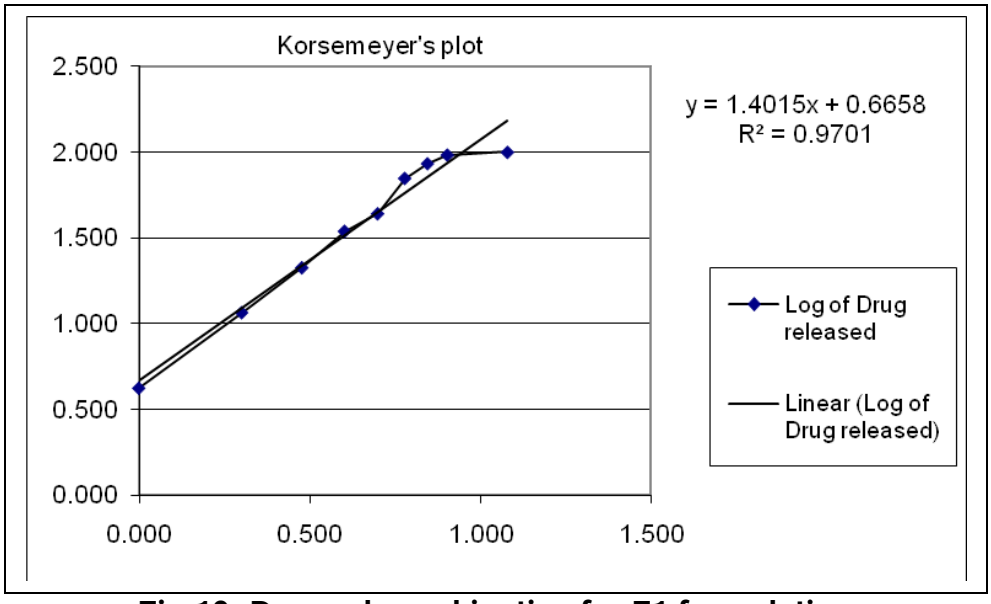

Fig 19: Drug release kinetics for F1 formulation

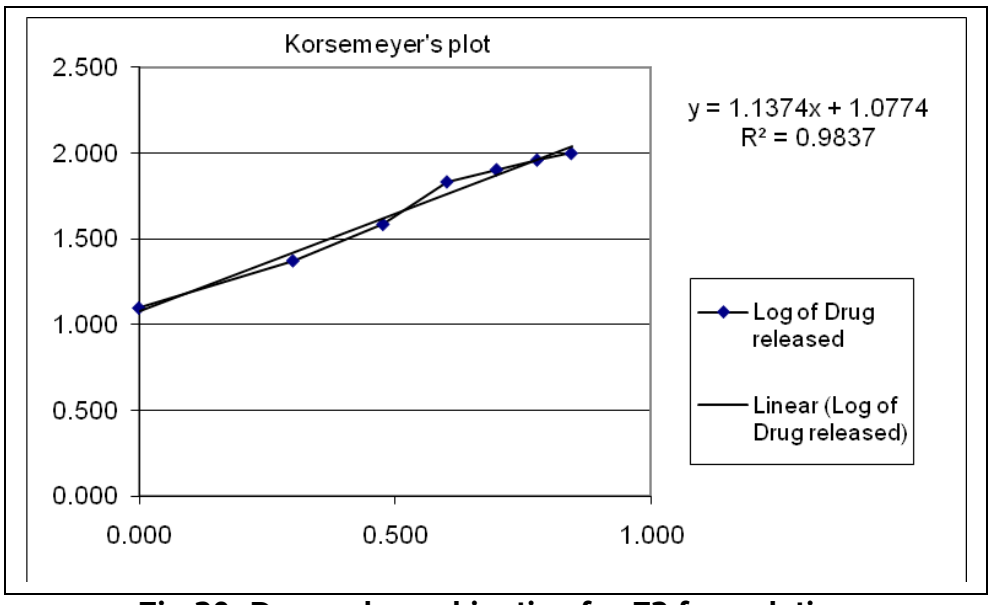

Fig 20: Drug release kinetics for F2 formulation

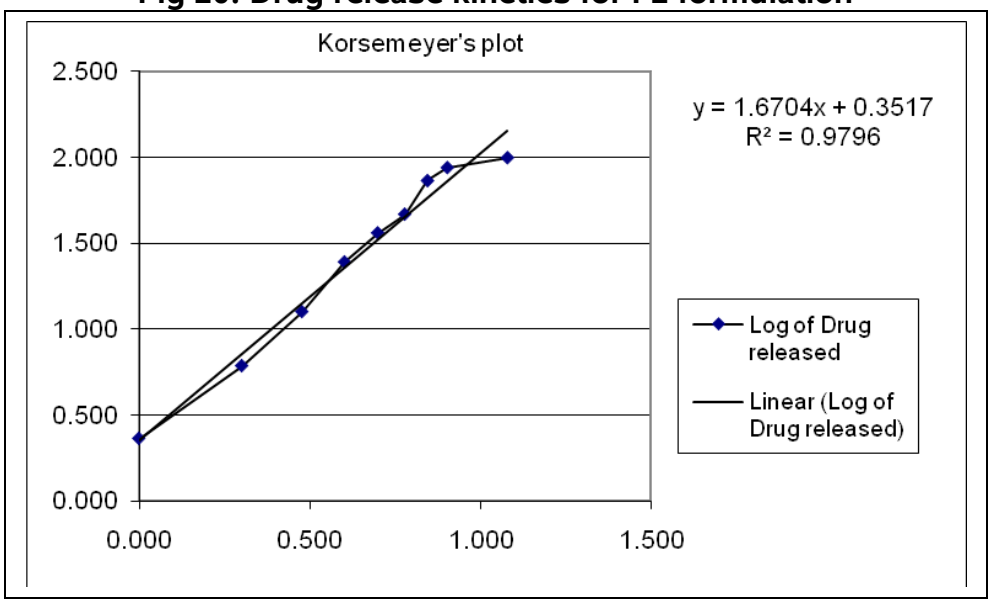

Fig 21: Drug release kinetics for F3 formulation

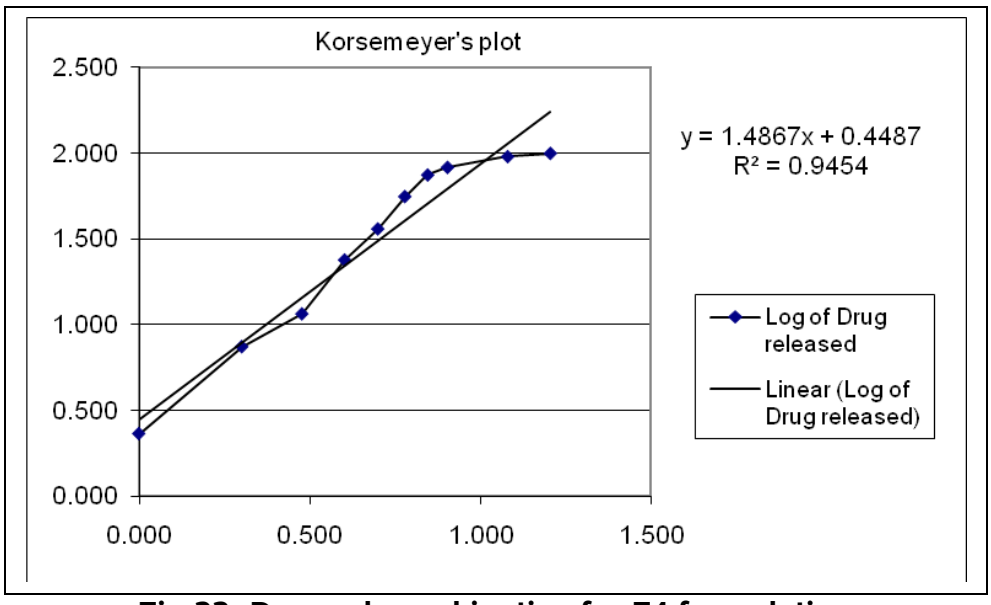

Fig 22: Drug release kinetics for F4 formulation

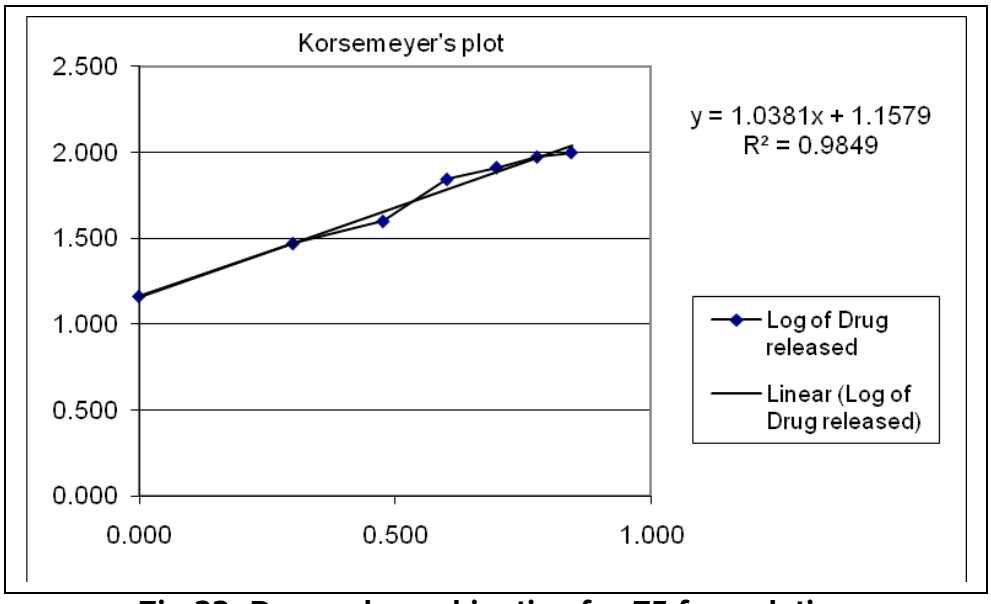

Fig 23: Drug release kinetics for F5 formulation

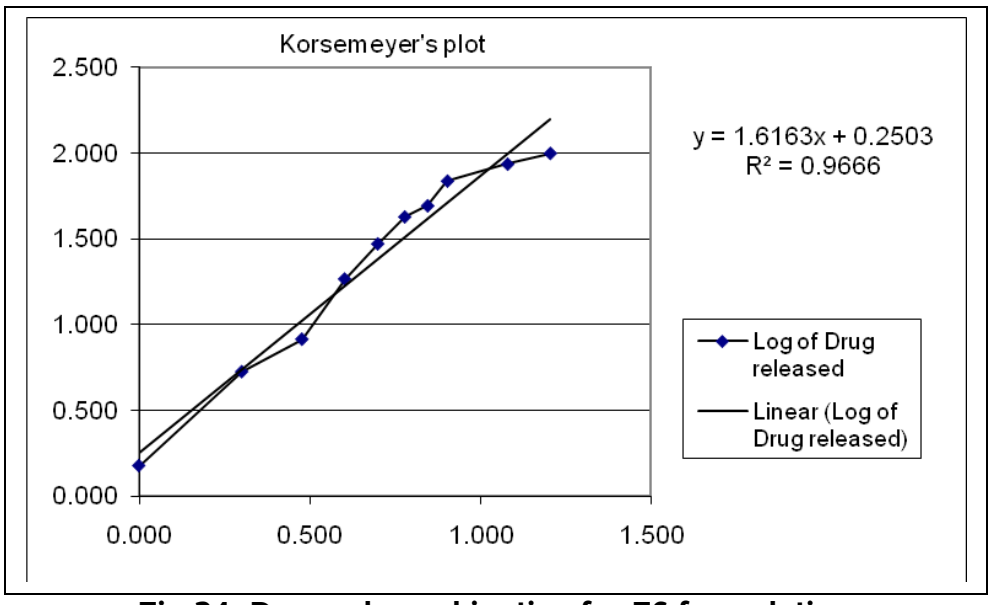

Fig 24: Drug release kinetics for F6 formulation

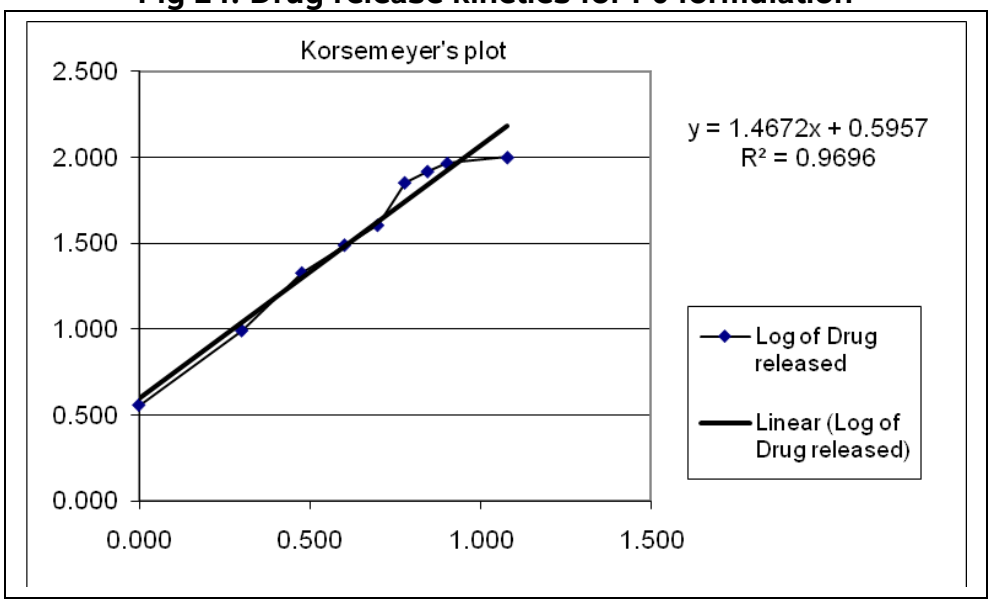

Fig 25: Drug release kinetics for F7 formulation

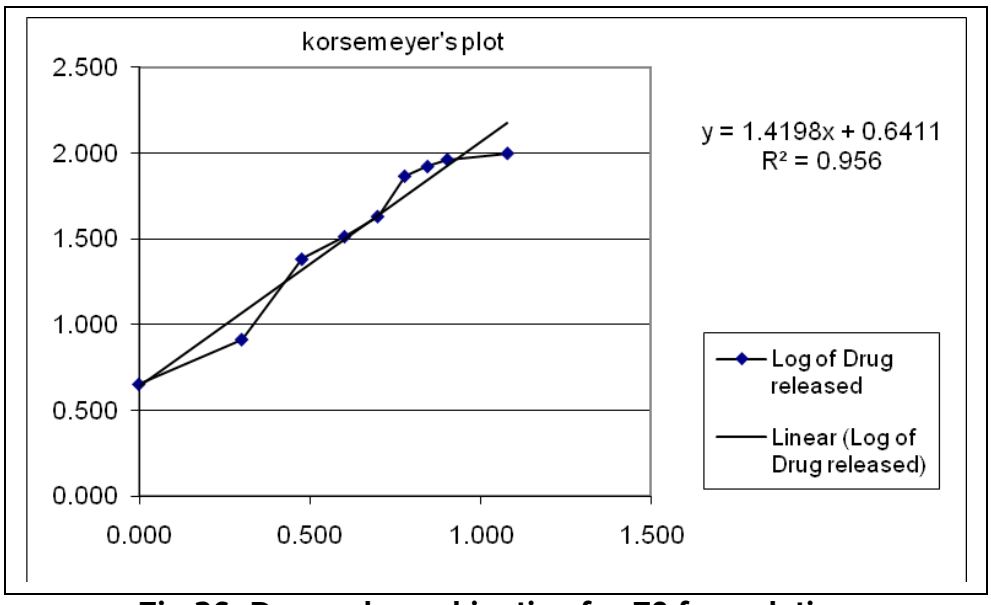

Fig 26: Drug release kinetics for F8 formulation

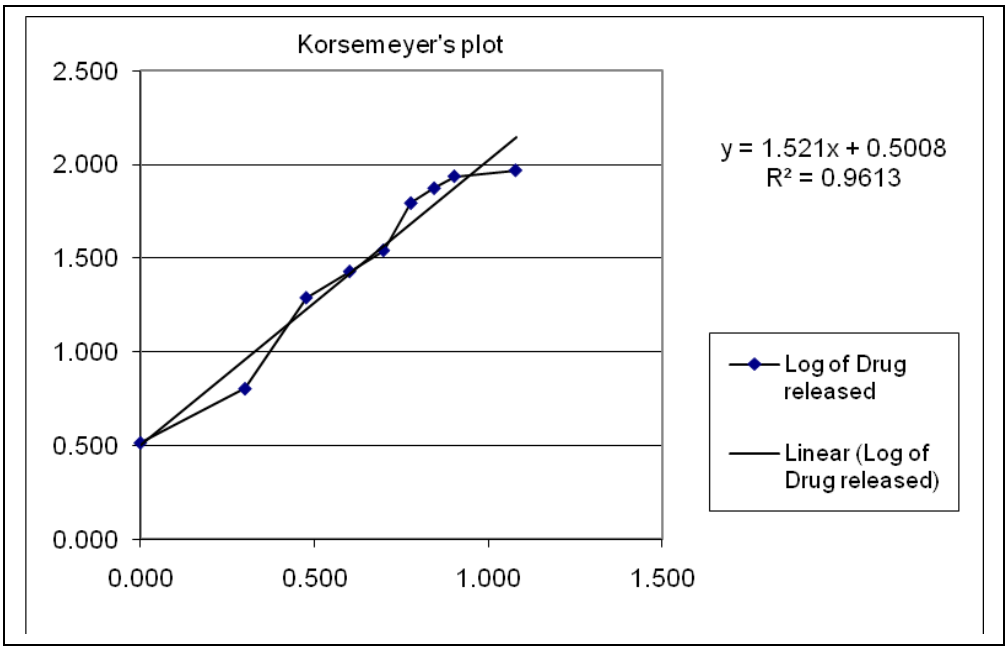

Fig 27: Drug release kinetics for F9 formulation

11. RESULTS AND DISCUSSION

The aim of this work was to develop a chronotherapeutic delivery of propranolol Hcl in the form of press-coated tablets. Totally nine different press-coated tablets of propranolol Hcl were formulated by using various proportion of different polymers such as HPMC, ethyl cellulose, xanthan gum and guar gum by direct compression method. Here we selected propranolol Hcl as a drug candidate because of most commonly used in the treatment of hypertension, arrhythmia and angina pectoris. In this study we develop a chronological dosage form to release the drug in the early morning between 3a.m to 6a.m because renin, cortisol, angiotensin, aldosterone were secreted in peak level, most of the cardiovascular disorders such as angina pectoris, sudden cardiac death, stroke occurs in this time, the designed formulation was planned to taken at bedtime and the focus was to optimally deliver the drug in higher amounts in the early morning hours and lower amount at night.

The prepared press-coated tablets (F1 to F9) were used for evaluation of compatibility studies, physico-chemical parameters such as hardness, friability, thickness, weight variation, content uniformity, *in vitro* release and *in vitro* release kinetics.

11.1 COMPATIBILITY STUDIES

The compatibility studies between the drugs and polymer were evaluated by using IR matching approach.

FT-IR Spectral Analysis

In IR studies, there was no appearance or disappearance of characteristics peaks in pure drug and drug excipient mixture. In propranolol Hcl IR spectrum, principal peaks were noticed at following wave numbers 1103, 1270, 772, 1580, 795, 1240cm^{-1} (KBr pellet). The IR spectra obtained are given in fig 6 to 8. This method confirms the absence of any chemical interaction between drug and polymer.

11.2 EVALUATION OF PROPRANOLOL HCL CONTROLLED ONSET EXTENDED RELEASE TABLETS

All the formulated propranolol controlled onset extended release tablets (F1-F9) have fulfilled official requirements for weight variation and drug content uniformity of formulation F4 and F9 shows maximum uniformity around 101% and 100.8% respectively (Table 18 and 19), hardness of the tablets in all the batches were found to be in the range of 4.9 to 5.7 kg/cm^2 (Table 16 and 17) and was satisfactory. The thickness of tablets ranges from 2.44mm to 3.16mm (Table 16 and 17) and the percentage weight loss in the friability test was found to be less than 1% in all formulations (Table 16 and 17) were found to be good quality fulfilling the tablets.

11.3 *IN VITRO* DISSOLUTION STUDIES

In vitro drug release of nine different press-coated tablets containing propranolol Hcl were determined by using USP dissolution apparatus containing 900 ml of hydrochloric acid buffer (pH 1.2) for first 2 hours and 900 ml of phosphate buffer (pH 6.8) for 22 hours at 100 rpm and 37 ± 0.5ºC. 5 ml of samples were taken, suitably diluted and analysed by UV-spectrophotometer at 290 nm. From the results the cumulative percentage drug release were calculated for each tablet using an equation obtained from standard graph.

From the results of *in vitro* studies all the prepared press-coated tablets (F1 to F9) were given a good release in the range of 92.7% w/v to 99.9% w/v. The formulation F2 [100mg of propranolol Hcl, EC:Xanthan gum (2:1)] and F5 [100mg of propranolol Hcl, EC:Guar gum (2:1)] were shown ideal release for chronotherpeutics. Because of having a lag time of 5 hours and maximum release of 99.9 % w/v and 99.4 % w/v respectively. The *in vitro* dissolution data are given in Table 22 and 25 and the graphs are shown in fig 10 and 13.

The profiles clearly indicate that the propranolol Hcl released from the press-coated tablet exhibited a unique release profile depending on the amount of xanthan gum and EC used and also HPMC polymer in core tablet contributes in drug release for prolonged period. The profile exhibited an induction period (lag time) followed by a prolonged drug

release throughout a day. The drug was released from the press-coated tablet after a lag period of 5-6 hours, depending upon the weight ratios of EC and xanthan gum. The swelling of the outer shell of press-coated tablets is a key factor to achieve the time-controlled delivery. The drug was released from the core tablet after rupturing, caused by the pressure build up with in the core system. Increasing the concentration of EC in the formulation of the outer shell, the lag time was increased. The lag time changed according to weight ratios of the EC and xanthan gum as follows.

F3>F1>F2

The dissolution profile of EC/guar gum was also similar to that of the dissolution profile of EC/ xanthan gum, showing a distinctive inducting lag followed by drug release. The lag time of the press coated tablets containing (1:1, 2:1 ,1:2) ratios of EC/guar gum was F6 > F4 > F5 respectively.

It is evident that the time lag of press-coated tablet changes by varying the amount of EC and xanthan gum and guar gum in the outer shell. The dissolution profile of F7 & F8 formulation shows that the release rate is independent of the drug concentration. Increase in amount of HPMC in core tablet (formulation F9) increases the lag time. The dissolution profile of all the formulated propranolol time controlled release tablets were reported in Table 20.

11.4 DRUG RELEASE KINETICS

In vitro data obtained for propranolol Hcl controlled onset extended release tablets were used to determine the Drug release kinetics. The drug release data of propranolol Hcl were fitted to model representing Korsmeyer's equation (log cumulative percentage of drug released vs. log time) kinetics to know the release mechanisms. The data were processed for regression analysis using MS-EXCEL statistical functions (Table 30). In our study *in vitro* release profiles of drug from all the formulations could be best expressed by Korsmeyer's equation showed highest linearity (R^2 0.984). where 'n' value is greater than 0.89 so it follows non-fickian diffusion. This explains why the drug diffuses at a comparatively slower rate.

12. CONCLUSION

The main focus of chronotherapeutic formulation of propranolol Hcl is to optimally deliver the drug in higher amounts in early morning hours (i.e. at time of greatest need) and lower amounts at night (i.e. when the need of drug is less). Because SBP and DBP rapidly rise in the early morning by at least 15 to 25 mm Hg and reach highest levels late in the day. Typically SBP and DBP decline in sleep by 10% to 20% from daytime.

From the results it was concluded formulation **F2** (EC:xanthan gum, 2:1) and **F5** (EC:guar gum, 2:1) shows lag time of 5 hours consistent with requirement for **chronotherapeutics** and the drug release was extended as shown in fig 22 and 25. The best lag time could be achieved by higher the concentration of EC in outer shell. The lag time could also be controlled by altering the weight ratios and viscosity grade of polymers.

- Hence COER Propranolol Hcl tablets can provide a useful means for timed release and may be helpful for BP patients with morning surge, which results in better compliance by patients and fewer side effects.
- In conclusion, the time lag of press-coated tablet could be modulated by choosing the type and amount of excipient used in the outer shell to achieve the time-controlled disintegration according to the time required The present study indicated that the lag time of the press-coated tablet can be suitably modulated by formulating the outer shell with ethyl cellulose and xanthan gum or guar gum.

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10 Tips to control Hypertension

1. **Maintain a healthy weight.**
2. **Exercise each day (Be physically active).**
3. **Eat more fruits, vegetables and low-fat dairy foods.**
4. **Eat foods with less sodium (salt).**
5. **Limit alcohol consumption.**
6. **Reduce your stress and learn to relax.**
7. **Avoid tobacco products and secondhand smoke.**
8. **Cut back on caffeine.**
9. **Get regular healthcare.**
10. **Take prescribed drugs as directed.**